

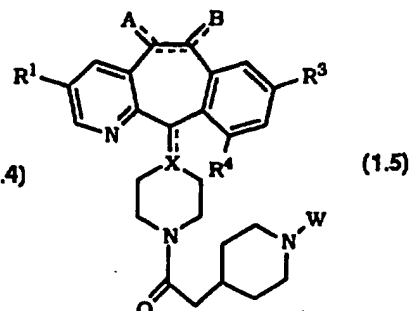
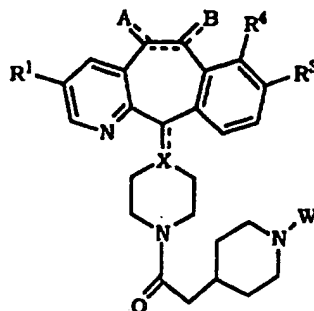
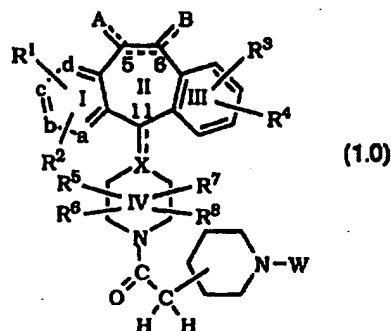


INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification C07D 401/04, A61K 31/55	A1	(11) International Publication Number: WO 98/11093 (43) International Publication Date: 19 March 1998 (19.03.98)
(21) International Application Number: PCT/US97/15907 (22) International Filing Date: 11 September 1997 (11.09.97) (30) Priority Data: 08/713,323 13 September 1996 (13.09.96) US (71) Applicant: SCHERING CORPORATION [US/US]; 2000 Galloping Hill Road, Kenilworth, NJ 07033 (US). (72) Inventors: TAVERAS, Arthur, G.; 43 Crestwood Road, Rockaway, NJ 07866 (US). MALLAMS, Alan, K.; 147 Kings Highway, Hackettstown, NJ 07840 (US). AFONSO, Adriano; 10 Woodmere Road, West Caldwell, NJ 07006 (US). (74) Agents: JEANETTE, Henry, C. et al.; Schering-Plough Corporation, Patent Dept. K-6-1 1990, 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 (US).		(81) Designated States: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CZ, EE, GE, HU, ID, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>

(54) Title: TRICYCLIC INHIBITORS OF FARNESYL PROTEIN TRANSFERASE**(57) Abstract**

Novel compounds of formula (1.0) are disclosed. Compounds of formula (1.0) are represented by the compounds of formulas (1.4) or (1.5) wherein R^1 , R^3 and R^4 are each independently selected from halo. Also disclosed are methods of inhibiting farnesyl protein transferase and the growth of abnormal cells, such as tumor cells.



AMY

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon	KR	Republic of Korea	PL	Poland		
CN	China	KZ	Kazakhstan	PT	Portugal		
CU	Cuba	LC	Saint Lucia	RO	Romania		
CZ	Czech Republic	LI	Liechtenstein	RU	Russian Federation		
DE	Germany	LK	Sri Lanka	SD	Sudan		
DK	Denmark	LR	Liberia	SE	Sweden		
EE	Estonia			SG	Singapore		

TRICYCLIC INHIBITORS OF FARNESYL PROTEIN TRANSFERASE

5

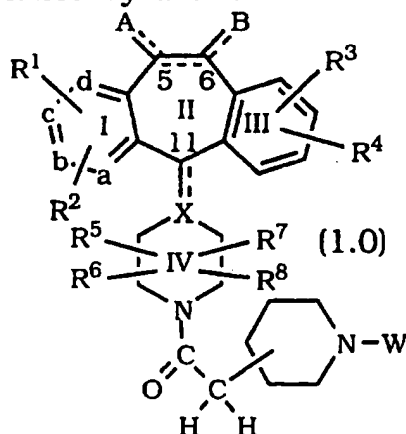
BACKGROUND

WO 95/10516, published April 20, 1995 discloses tricyclic compounds useful for inhibiting farnesyl protein transferase.

In view of the current interest in inhibitors of farnesyl protein transferase, a welcome contribution to the art would be compounds useful for the inhibition of farnesyl protein transferase. Such a contribution is provided by this invention.

SUMMARY OF THE INVENTION

This invention provides compounds useful for the inhibition of farnesyl protein transferase (FPT). The compounds of this invention are represented by the formula:

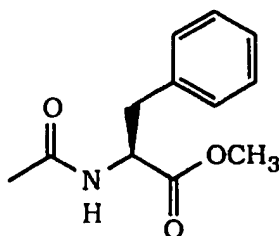


or a pharmaceutically acceptable salt or solvate thereof, wherein:
one of a, b, c and d represents N or NR⁹ wherein R⁹ is O⁻, -CH₃ or -(CH₂)_nCO₂H wherein n is 1 to 3, and the remaining a, b, c and d groups represent CR¹ or CR²; or

each of a, b, c, and d are independently selected from CR¹ or CR²;

each R¹ and each R² is independently selected from H, halo, -CF₃, -OR¹⁰ (e.g., -OCH₃), -COR¹⁰, -SR¹⁰ (e.g., -SCH₃ and -SCH₂C₆H₅), -S(O)_tR¹¹ (wherein t is 0, 1 or 2, e.g., -SOCH₃ and -SO₂CH₃), -SCN, -N(R¹⁰)₂, -NR¹⁰R¹¹, -NO₂, -OC(O)R¹⁰, -CO₂R¹⁰, -OCO₂R¹¹, -CN, -NHC(O)R¹⁰, -NHSO₂R¹⁰, -CONHR¹⁰, -CONHCH₂CH₂OH, -NR¹⁰COOR¹¹,

- 2 -



-SR¹¹C(O)OR¹¹ (e.g., -SCH₂CO₂CH₃), -SR¹¹N(R⁷⁵)₂ wherein each R⁷⁵ is independently selected from H and -C(O)OR¹¹ (e.g., -S(CH₂)₂NHC(O)O-t-butyl and -S(CH₂)₂NH₂), benzotriazol-1-yloxy, tetrazol-5-ylthio, or substituted tetrazol-5-ylthio (e.g., alkyl substituted tetrazol-5-ylthio such as 1-methyl-tetrazol-5-ylthio), alkynyl, alkenyl or alkyl, said alkyl or alkenyl group optionally being substituted with halo, -OR¹⁰ or -CO₂R¹⁰;

R³ and R⁴ are the same or different and each independently represents H, any of the substituents of R¹ and R², or R³ and R⁴ taken together represent a saturated or unsaturated C₅-C₇ fused ring to the benzene ring (Ring III);

R⁵, R⁶, R⁷ and R⁸ each independently represents H, -CF₃, -COR¹⁰, alkyl or aryl, said alkyl or aryl optionally being substituted with -OR¹⁰, -SR¹⁰, -S(O)_tR¹¹, -NR¹⁰COOR¹¹, -N(R¹⁰)₂, -NO₂, -COR¹⁰, -OCOR¹⁰, -OCO₂R¹¹, -CO₂R¹⁰, OPO₃R¹⁰ or R⁵ is combined with R⁶ to represent =O or =S and/or R⁷ is combined with R⁸ to represent =O or =S;

R¹⁰ represents H, alkyl, aryl, or aralkyl (e.g., benzyl);
R¹¹ represents alkyl or aryl;

X represents N, CH or C, which C may contain an optional double bond (represented by the dotted line) to carbon atom 11;

the dotted line between carbon atoms 5 and 6 represents an optional double bond, such that when a double bond is present, A and B independently represent -R¹⁰, halo, -OR¹¹, -OCO₂R¹¹ or -OC(O)R¹⁰, and when no double bond is present between carbon atoms 5 and 6, A and B each independently represent H₂, -(OR¹¹)₂; H and halo, dihalo, alkyl and H, (alkyl)₂, -H and -OC(O)R¹⁰, H and -OR¹⁰, =O, aryl and H, =NOR¹⁰ or -O-(CH₂)_p-O- wherein p is 2, 3 or 4; and

W represents a heteroaryl, aryl, heterocyloalkyl or cycloalkyl group.

- 3 -

The compounds of this invention: (i) potently inhibit farnesyl protein transferase, but not geranylgeranyl protein transferase I, in vitro; (ii) block the phenotypic change induced by a form of transforming Ras which is a farnesyl acceptor but not by a form of transforming Ras engineered to be a geranylgeranyl acceptor; (iii) block intracellular processing of Ras which is a farnesyl acceptor but not of Ras engineered to be a geranylgeranyl acceptor; and (iv) block abnormal cell growth in culture induced by transforming Ras.

The compounds of this invention inhibit farnesyl protein transferase and the farnesylation of the oncogene protein Ras. Thus, this invention further provides a method of inhibiting farnesyl protein transferase, (e.g., ras farnesyl protein transferase) in mammals, especially humans, by the administration of an effective amount of the tricyclic compounds described above. The administration of the compounds of this invention to patients, to inhibit farnesyl protein transferase, is useful in the treatment of the cancers described below.

This invention provides a method for inhibiting or treating the abnormal growth of cells, including transformed cells, by administering an effective amount of a compound of this invention. Abnormal growth of cells refers to cell growth independent of normal regulatory mechanisms (e.g., loss of contact inhibition). This includes the abnormal growth of: (1) tumor cells (tumors) expressing an activated Ras oncogene; (2) tumor cells in which the Ras protein is activated as a result of oncogenic mutation in another gene; and (3) benign and malignant cells of other proliferative diseases in which aberrant Ras activation occurs.

This invention also provides a method for inhibiting or treating tumor growth by administering an effective amount of the tricyclic compounds, described herein, to a mammal (e.g., a human) in need of such treatment. In particular, this invention provides a method for inhibiting or treating the growth of tumors expressing an activated Ras oncogene by the administration of an effective amount of the above described compounds. Examples of tumors which may be inhibited or treated include, but are not limited to, lung cancer (e.g., lung adenocarcinoma), pancreatic

- 4 -

cancers (e.g., pancreatic carcinoma such as, for example, exocrine pancreatic carcinoma), colon cancers (e.g., colorectal carcinomas, such as, for example, colon adenocarcinoma and colon adenoma), myeloid leukemias (for example, acute
5 myelogenous leukemia (AML)), thyroid follicular cancer, myelodysplastic syndrome (MDS), bladder carcinoma, epidermal carcinoma, breast cancer and prostate cancer.

It is believed that this invention also provides a method for inhibiting or treating proliferative diseases, both benign and
10 malignant, wherein Ras proteins are aberrantly activated as a result of oncogenic mutation in other genes--i.e., the Ras gene itself is not activated by mutation to an oncogenic form--with said inhibition or treatment being accomplished by the administration of an effective amount of the tricyclic compounds described
15 herein, to a mammal (e.g., a human) in need of such treatment. For example, the benign proliferative disorder neurofibromatosis, or tumors in which Ras is activated due to mutation or overexpression of tyrosine kinase oncogenes (e.g., neu, src, abl, lck, and fyn), may be inhibited or treated by the tricyclic
20 compounds described herein.

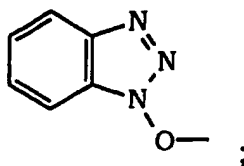
The tricyclic compounds useful in the methods of this invention inhibit or treat the abnormal growth of cells. Without wishing to be bound by theory, it is believed that these compounds may function through the inhibition of G-protein
25 function, such as ras p21, by blocking G-protein isoprenylation, thus making them useful in the treatment of proliferative diseases such as tumor growth and cancer. Without wishing to be bound by theory, it is believed that these compounds inhibit ras farnesyl protein transferase, and thus show antiproliferative activity
30 against ras transformed cells.

DETAILED DESCRIPTION OF THE INVENTION

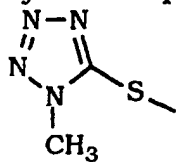
As used herein, the following terms are used as defined below unless otherwise indicated:

35 MH⁺-represents the molecular ion plus hydrogen of the molecule in the mass spectrum;
benzotriazol-1-yloxy represents

- 5 -



1-methyl-tetrazol-5-ylthio represents



acyl-represents represents -C(O)-alkyl, -C(O)-alkenyl,
 5 -C(O)-alkynyl, -C(O)-cycloalkyl, -C(O)-cycloalkenyl or -C(O)-
 cycloalkynyl;

alkenyl-represents straight and branched carbon chains
 having at least one carbon to carbon double bond and containing
 from 2 to 12 carbon atoms, preferably from 2 to 6 carbon atoms
 10 and most preferably from 3 to 6 carbon atoms;

alkynyl-represents straight and branched carbon chains
 having at least one carbon to carbon triple bond and containing
 from 2 to 12 carbon atoms, preferably from 2 to 6 carbon atoms;

alkyl-(including the alkyl portions of alkoxy, aralkyl and
 15 heteroarylalkyl)-represents straight and branched carbon chains
 and contains from one to twenty carbon atoms, preferably one to
 six carbon atoms;

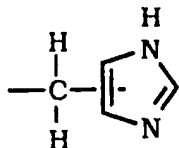
aralkyl-represents an aryl group, as defined below, bound
 to an alkyl group, as defined above, preferably the alkyl group is
 20 -CH₂-, (e.g., benzyl);

aryl (including the aryl portion of aralkyl, aryloxy and
 arylalkyloxy)-represents a carbocyclic group containing from 6 to
 15 carbon atoms and having at least one aromatic ring (e.g., aryl
 is a phenyl ring), with all available substitutable carbon atoms of
 25 the carbocyclic group being intended as possible points of
 attachment, said carbocyclic group being optionally substituted
 (e.g., 1 to 3) with one or more of halo, alkyl, hydroxy, alkoxy,
 phenoxy, CF₃, amino, alkylamino, dialkylamino, -COOR¹⁰ or -NO₂;

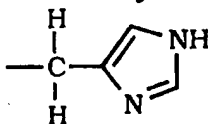
aroyl - represents C(O)-aryl wherein aryl is as defined
 30 above;

-CH₂-imidazolyl represents an imidazolyl group bound by
 any substitutable carbon of the imidazole ring to a -CH₂-, that is:

- 6 -



such as -CH₂-(2-, 4- or 5-)imidazolyl, for example



cycloalkyl-represents saturated carbocyclic rings

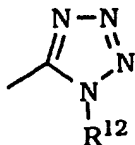
- 5 branched or unbranched of from 3 to 20 carbon atoms, preferably 3 to 7 carbon atoms;

cycloalkenyl - represents a carbocyclic ring having from 3 to 8 carbon atoms and at least one carbon to carbon double bond in the ring;

- 10 cycloalkynyl - represents a carbocyclic ring having at least 8 carbon atoms, preferably 8 to 15 carbon atoms and at least one carbon to carbon triple bond in such ring;

halo-represents fluoro, chloro, bromo and iodo;

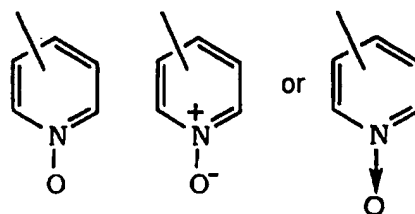
- heteroaryl-represents cyclic groups, optionally substituted
 15 with R³ and R⁴, having at least one heteroatom selected from O, S or N, said heteroatom interrupting a carbocyclic ring structure and having a sufficient number of delocalized pi electrons to provide aromatic character, with the aromatic heterocyclic groups preferably containing from 2 to 14 carbon atoms;
 20 examples include: (1) thienyl (e.g., 2- or 3-thienyl); (2) imidazolyl (e.g., (2-, 4- or 5-) imidazolyl); (3) triazolyl (e.g., 3- or 5- [1,2,4-triazolyl], 3-amino-1,2,4-triazolyl); (4) tetrazolyl; (5) substituted tetrazolyl, such as



- 25 wherein R¹² represents: (a) aryl (e.g., phenyl), (b) aralkyl (e.g., benzyl, (c) heteroarylalkyl (heteroaralkyl), (d) alkyl (e.g., methyl), or (e) substituted derivatives thereof (e.g, wherein said substituents are selected from the group consisting of: -OR¹¹, -N(R¹⁰)₂, alkyl, aryl, and heteroaryl), provided that said
 30 substituent is not on an α carbon of an alkyl group of (d) (i.e., when R¹² is alkyl said substituent of (e) is not on the α carbon of

- 7 -

said alkyl group); (6) thiazolyl (or thiazyl) (e.g., 2-, 4- or 5-thiazolyl); (7) pyrimidinyl (e.g., 2-, 4- or pyrimidinyl); (8) pyrazinyl (e.g., 2-pyrazinyl); (9) pyridazinyl (e.g., 3- or 4-pyridazinyl); (10) triazinyl (e.g., 2-, 4- or 6-[1,3,5-triazinyl]); (11) 3- or 5-[1,2,4-thiadizolyl]; (12) benzoxazolyl (e.g., 2-benzoxazolyl); (13) N-substituted 3-pyrazolyl, (14) oxazolyl (e.g., 2-, 4- or 5-oxazolyl); (15) 2-, or 4-pyridyl or pyridyl N-oxide (optionally substituted with R³ and R⁴), wherein pyridyl N-oxide can be represented as:



10

(16) isoxazolyl; (17) benzisoxazolyl; (18) benzimidazolyl; (19) the radicals derived from purine (e.g., 2-, 6-, or 8-); (20) the radicals derived from adenine (6- or 8- adeninyl), (21) isoquinolinyl (2- or 8-); (22) quinolinyl (2- or 4-); (23) pyridopyrazinyl (2-, 3-, 5- or 7-); (24) naphthyridinyl (2-, 4-, 5-, or 7-); (25) isothiazolyl; (26) furazanyl; and (27) oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 5-amino-1,2,4-oxadiazolyl, and 3-amino-1,2,4-oxadiazolyl).

heteroarylalkyl-represents a heteroaryl group, as defined above, bound to an alkyl group, as defined above, preferably the alkyl group is -CH₂- (e.g., -CH₂-(4- or 5-)imidazolyl);

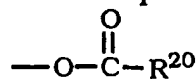
heterocycloalkyl-represents a saturated, branched or unbranched carbocyclic ring containing from 3 to 15 carbon atoms, preferably from 4 to 6 carbon atoms, which carbocyclic ring is interrupted by 1 to 3 hetero groups selected from -O-, -S-, -NR¹⁰- (wherein R¹⁰ is as defined above) or -NR³²- wherein R³² is selected from the group consisting of:

(1) heteroaryl, (2) heterocycloalkyl, (3) acyl, (4) aroyl, (5) alkoxycarbonyl, (6) aryloxy carbonyl, (7) arylalkyloxy carbonyl, (8) sulfonyl [e.g., -SO₂R¹⁴ wherein R¹⁴ is selected from the group consisting of: alkyl, heteroaryl, aralkyl and heteroaralkyl] and (9) phosphonyl [e.g., -P(O)(OR¹⁶)₂- wherein R¹⁶ is, for example, alkyl (e.g., ethyl)],

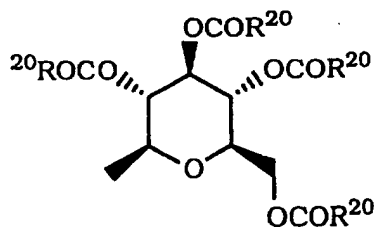
suitable heterocycloalkyl groups include:

- (1) tetrahydrofuranyl (e.g., 2- or 3-tetrahydrofuranyl),
- (2) tetrahydrothienyl e.g., (2- or 3- tetrahydrothienyl),
- (3) piperidiny (e.g., 2-, 3- or 4-piperidiny),
- (4) pyrrolidiny (e.g., 2- or 3-pyrrolidiny),
- (5) piperaziny (e.g., 2- or 3-piperaziny),
- (6) dioxany (e.g., 2-dioxany),
- (7) tetrahydropyrany,

(8) pyranosidyl (i.e., the radical derived from pyranosides), for example a pyranose (e.g., glucopyranose, mannopyranose and galactopyranose) wherein one or more -OH groups are acylated to produce an

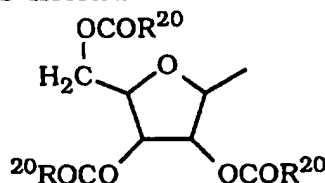


(also represented as -OCOR²⁰ or -OC(O)R²⁰) (e.g., -OCOCH₃) group, examples include the glucosides (glucosidyls)



wherein R²⁰ is alkyl (e.g., methyl);

(9) furanosidyl (i.e., the radical derived from furanosides, e.g., ribofuranose and deoxyribofuranose), for example a furanose wherein one or more -OH groups are acylated to produce an -O-(O)CR²⁰ (e.g., -O-(O)CCH₃) group, examples include the furanosides



wherein R²⁰ is as defined above;

(10) the radical from trimethylene oxide, e.g., 3-oxetanyl;

(11) the radical from azetidine;

(12) 1-azacycloheptanyl;

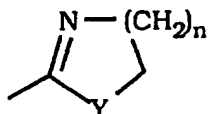
(13) perhydroisoquinolinyl;

(14) decahydroquinolinyl;

(15) 1,4-dioxanyl;

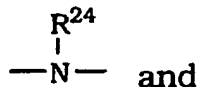
- 9 -

- (16) 1,3-dioxanyl;
 (17) thiazolidinyl; and
 (18) cyclic guanidines (Y is NR²²) or cyclic amidines (Y is CH₂) of the formula:



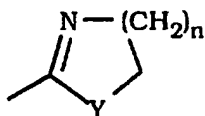
5

wherein n is 1 or 2; Y is



R²⁴ is selected from the group consisting of: H, alkyl aryl and aralkyl, examples of the cyclic guanidines include the group of the formula:

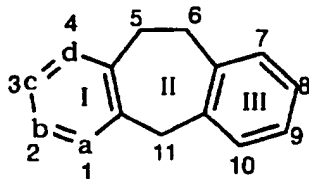
10



wherein Y is -NR²⁴ and R²⁴ is H, and n is 1; examples of cyclic amidines include compounds wherein Y is CH₂ and n is 1.

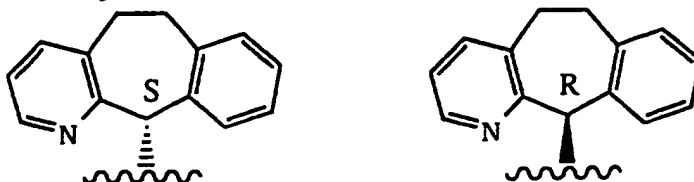
- 15 The following solvents and reagents are referred to herein by the abbreviations indicated: ethanol (EtOH); methanol (MeOH); acetic acid (HOAc or AcOH); ethyl acetate (EtOAc); N,N-dimethylformamide (DMF); trifluoroacetic acid (TFA); trifluoroacetic anhydride (TFAA); 1-hydroxybenzotriazole (HOBT);
 20 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (DEC); diisobutylaluminum hydride (DIBAL); and 4-methylmorpholine (NMM).

Reference to the position of the substituents R¹, R², R³, and R⁴ is based on the numbered ring structure:

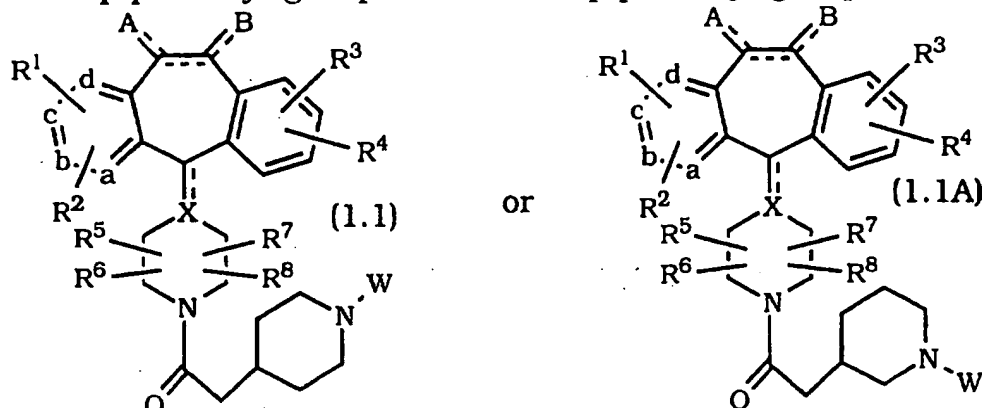


25

Those skilled in the art will also appreciate that the S and R stereochemistry at the C-11 bond are:

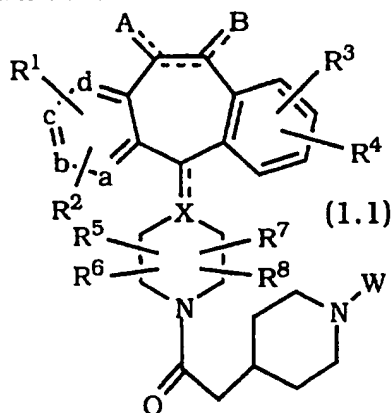


Compounds of Formula 1.0 include compounds wherein the bottom piperidinyl group is a 4- or 3-piperidinyl group, i.e.,



Compounds of Formula 1.0 include compounds wherein R² and R⁴ are H, and R¹ and R³ are halo (preferably independently selected from Br or Cl). For example, R¹ is Br and R³ is Cl. These compounds include compounds wherein R¹ is in the 3-position and R³ is in the 8-position, e.g., 3-Br and 8-Cl. Compounds of Formula 1.0 also include compounds wherein R² is H, and R¹, R³ and R⁴ are halo (preferably independently selected from Br or Cl).

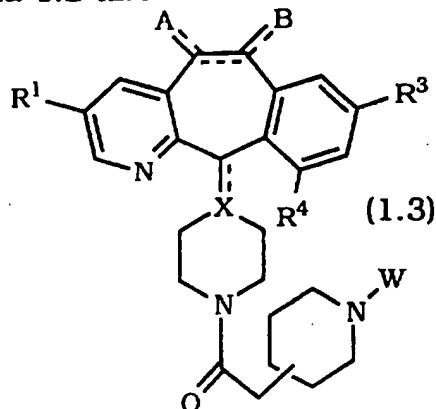
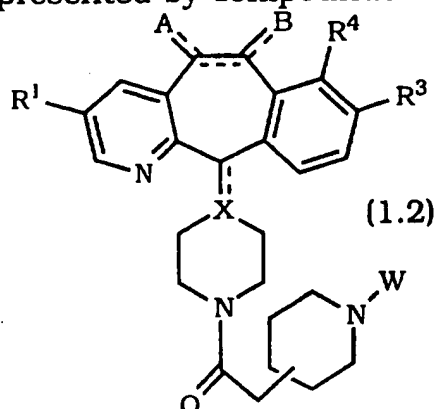
Preferably, compounds of Formula 1.0 are represented by compounds of Formula 1.1:



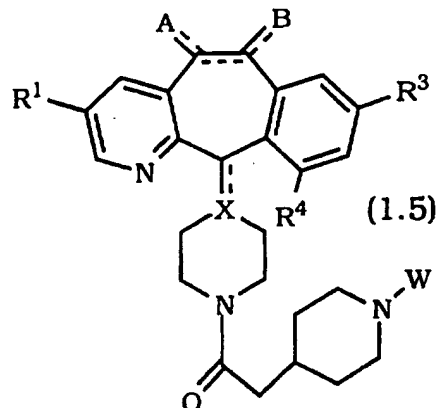
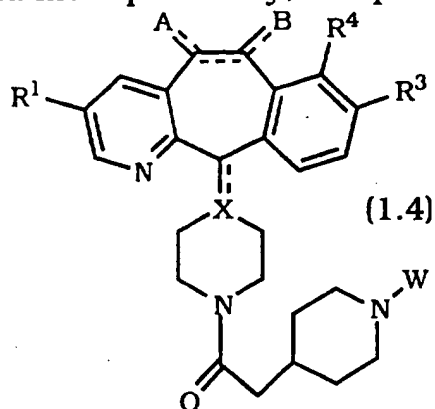
15 wherein all substituents are as defined for Formula 1.0.

Preferably, R² is H and R¹, R³ and R⁴ are halo; a is N and b, c and d are carbon; A and B are each H₂; the optional bond between C5 and C6 is absent; X is CH; and R⁵, R⁶, R⁷ and R⁸ are H. More preferably, R¹, R³ and R⁴ are independently selected from Br or Cl. Most preferably, R¹ is Br, and R³ and R⁴ are independently selected from Cl and Br.

More preferably, compounds of Formula 1.0 are represented by compounds of Formula 1.2 and Formula 1.3:



and most preferably, compounds of Formulas 1.4 and 1.5

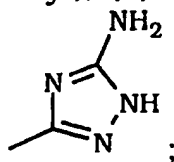


5

wherein R^1 , R^3 and R^4 are each independently selected from halo, preferably, Br or Cl; and A, B, X and W are as defined for Formula 1.0. More preferably, A and B are each H_2 ; the optional bond between C5 and C6 is absent; and X is CH. Most preferably,

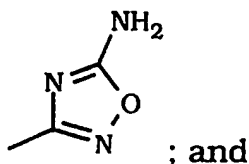
10 R^1 is Br; R^3 and R^4 are independently Br or Cl, and still more preferably R^3 is Cl and R^4 is Br; A and B are each H_2 ; the optional bond between C5 and C6 is absent; X is CH; and R^5 , R^6 , R^7 and R^8 are H.

- Examples of preferred heteroaryl groups for W include: (1)
- 15 1-phenyl-1H-tetrazol-5-yl; (2) pyridyl (e.g., 2- or 4-pyridyl); (3) thiazolyl (e.g., 2-thiazolyl); (4) benzoxazolyl (e.g., 2-benzoxazolyl); (5) pyrimidinyl (e.g., 2-pyrimidinyl); (6) 3-amino-1,2,4-triazolyl

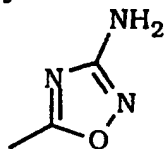


- (7) 5-amino-1,2,4-oxadiazolyl

- 12 -

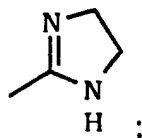


(8) 3-amino-1,2,4-oxadiazolyl

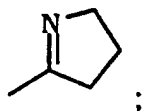


Examples of heterocycloalkyl groups for W usually include:

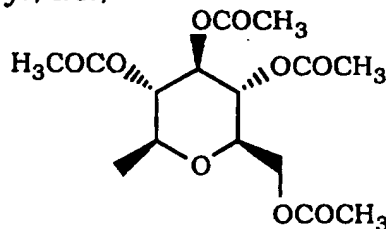
5 (1) cyclic guanidines, such as



(2) cyclic amidines, such as



(3) five and six membered heterocycloalkyl rings; and (4)
 10 pyranosidyl (from pyranosides), such as, 2,3,4,6-tetra-O-acetyl-1-beta-D-glucopyranosyl, i.e.,



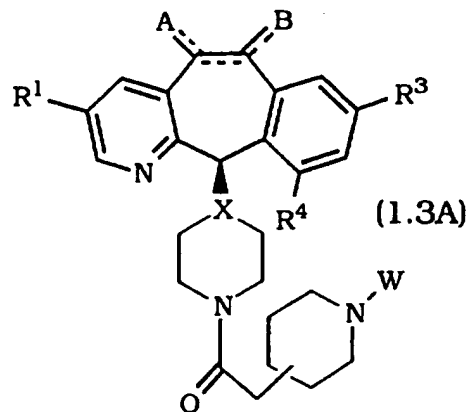
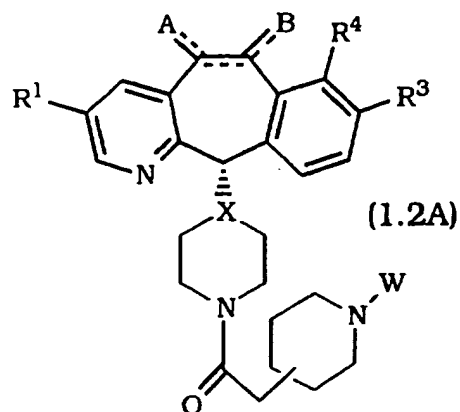
Preferred heterocycloalkyl groups include 2,3,4,6-tetra-O-acetyl-1-beta-D-glucopyranosyl.

15 Examples of cycloalkyl groups for W generally include: cyclopropane, cyclopentane, and cyclohexane. Thus, W usually includes cyclopentane.

Examples of aryl groups for W generally include phenyl.

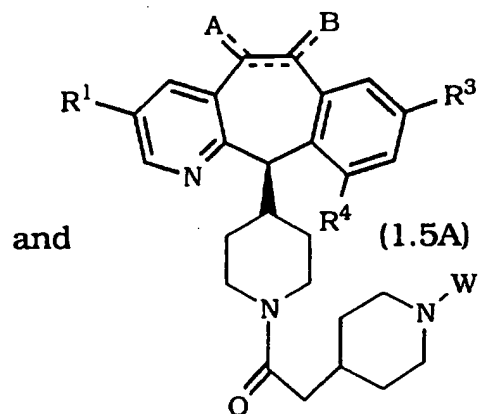
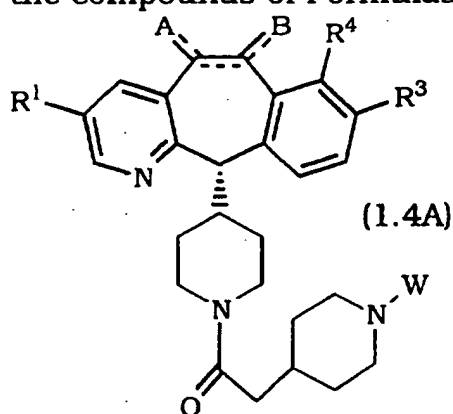
Compounds of Formulas 1.2A and 1.3A:

- 13 -



are preferred when X is CH or N, and R¹, R³ and R⁴ are halo.

The preferred compounds of this invention are represented by the compounds of Formulas:

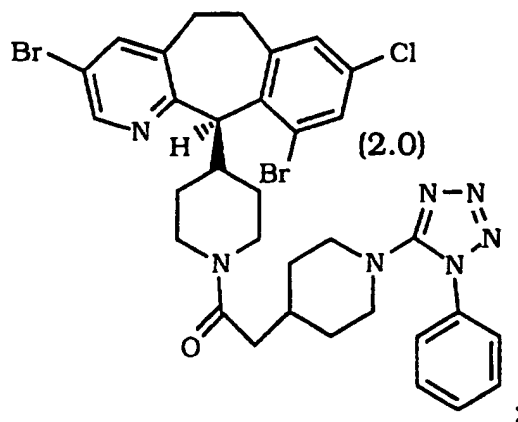


and

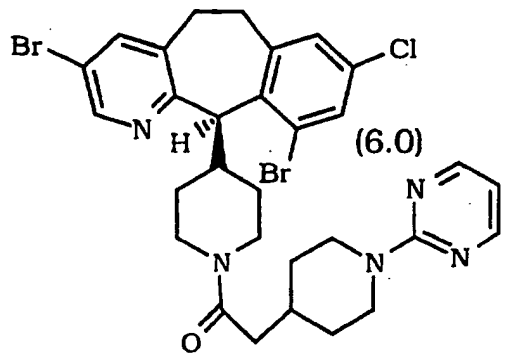
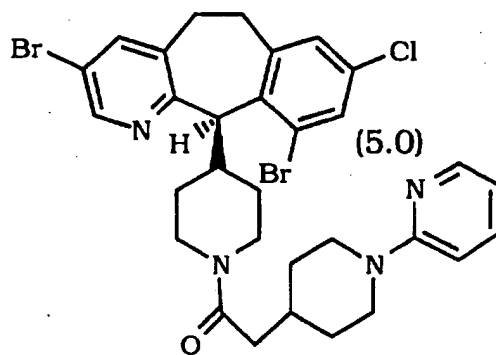
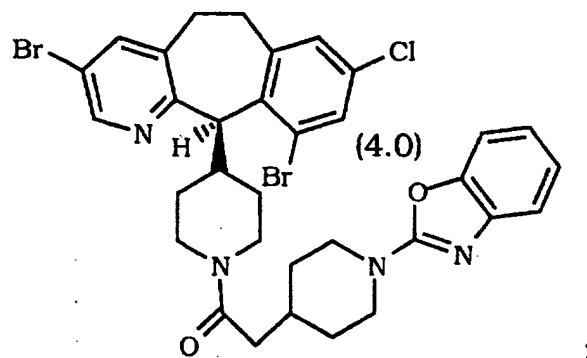
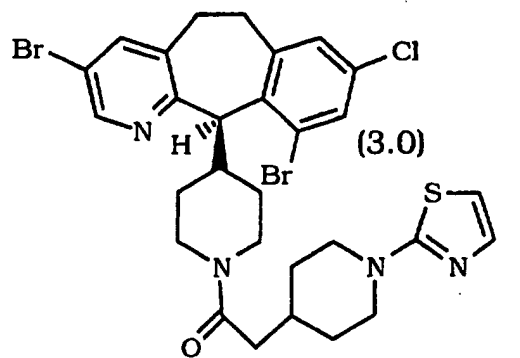
5

wherein R¹, R³ and R⁴ are halo and the remaining substituents are as defined above, with the compounds of Formula 1.5A being more preferred.

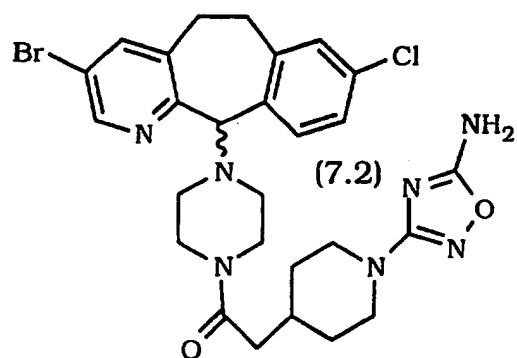
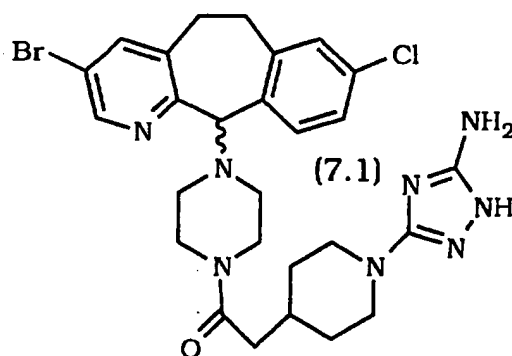
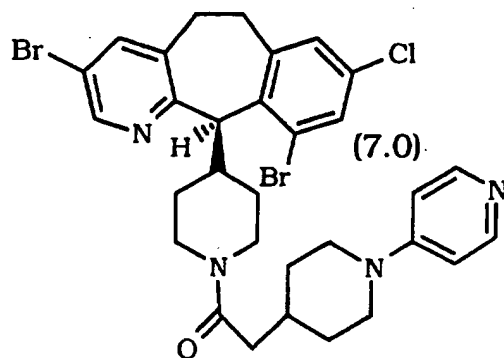
Representative compounds of Formula 1.0 wherein W is
10 heteroaryl include:



- 14 -

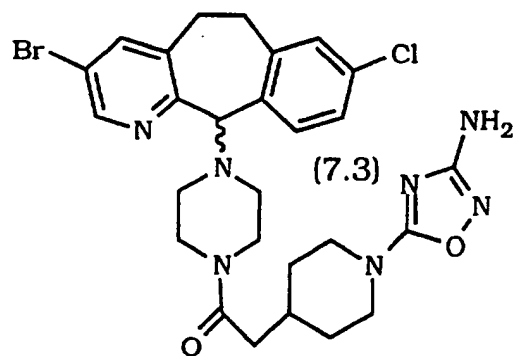


- 15 -



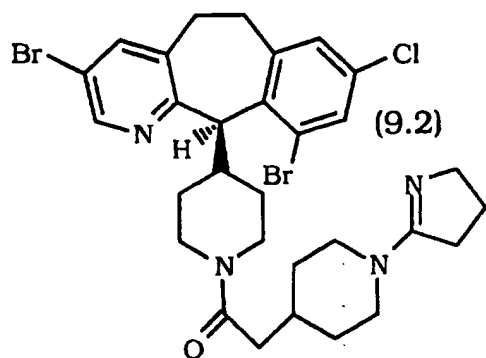
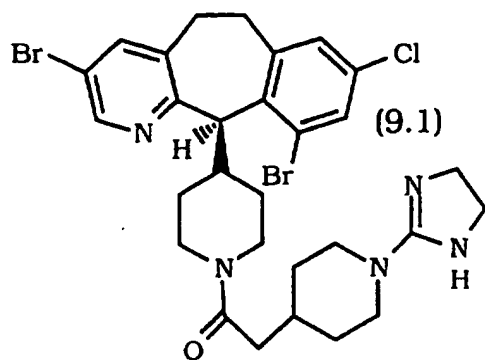
5

; and

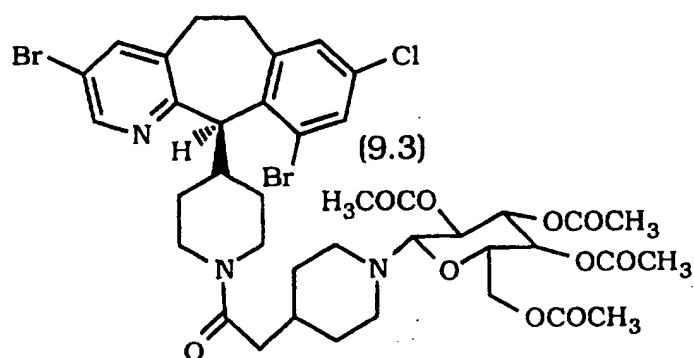


Representative compounds of Formula 1.0 wherein W is
 10 heterocycloalkyl include:

- 16 -

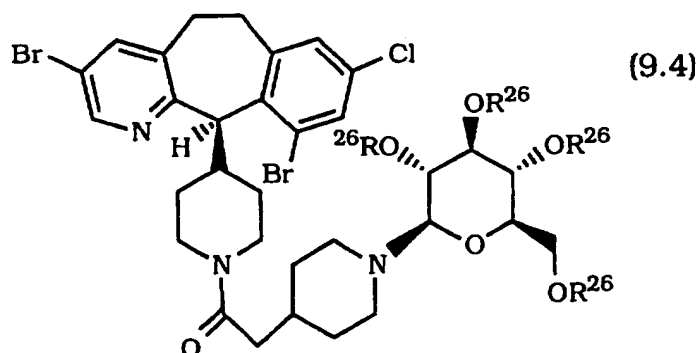


and



5

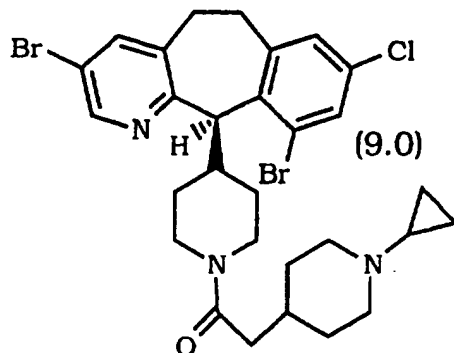
Those skilled in the art will appreciate that Formula 9.3 can also be represented as



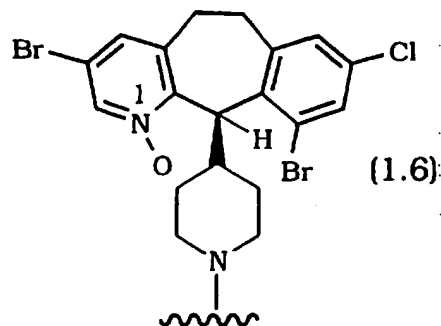
10 wherein R^{26} represents $-C(O)CH_3$.


- 17 -

Representative compounds of Formula 1.0 wherein W is cycloalkyl include:



The compounds of this invention also include the 1-N-oxides--i.e, for example, compounds of the the formula:



wherein  represents the remainder of the compound, or pharmaceutically acceptable salts or solvates thereof.

Optical rotation of the compounds ((+)- or (-)-) are measured in methanol or ethanol at 25°C.

This invention includes the above compounds in the amorphous state or in the crystalline state.

Lines drawn into the ring systems indicate that the indicated bond may be attached to any of the substitutable ring carbon atoms.

Certain compounds of the present invention may exist in different isomeric forms (e.g., enantiomers or diastereoisomers) including atropisomers (i.e., compounds wherein the 7-membered ring is in a fixed conformation such that the 11-carbon atom is positioned above or below the plane of the fused benzene rings due to the presence of a 10-bromo substituent). The invention contemplates all such isomers both in pure form and in admixture, including racemic mixtures. Enol forms are also included.

- 18 -

Certain tricyclic compounds will be acidic in nature, e.g. those compounds which possess a carboxyl or phenolic hydroxyl group. These compounds may form pharmaceutically acceptable salts. Examples of such salts may include sodium, potassium, 5 calcium, aluminum, gold and silver salts. Also contemplated are salts formed with pharmaceutically acceptable amines such as ammonia, alkyl amines, hydroxyalkylamines, N-methylglucamine and the like.

Certain basic tricyclic compounds also form 10 pharmaceutically acceptable salts, e.g., acid addition salts. For example, the pyrido-nitrogen atoms may form salts with strong acid, while compounds having basic substituents such as amino groups also form salts with weaker acids. Examples of suitable acids for salt formation are hydrochloric, sulfuric, phosphoric, 15 acetic, citric, oxalic, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic and other mineral and carboxylic acids well known to those in the art. The salts are prepared by contacting the free base form with a sufficient amount of the desired acid to produce a salt in the conventional 20 manner. The free base forms may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute aqueous NaOH, potassium carbonate, ammonia and sodium bicarbonate. The free base forms differ from their respective salt forms somewhat in certain physical properties, such as solubility 25 in polar solvents, but the acid and base salts are otherwise equivalent to their respective free base forms for purposes of the invention.

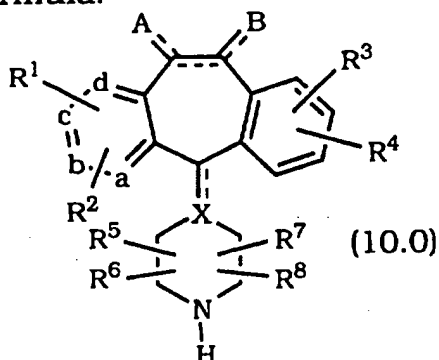
All such acid and base salts are intended to be pharmaceutically acceptable salts within the scope of the 30 invention and all acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of the invention.

Compounds of the invention may be prepared according to the procedures described in WO 95/10516 published April 20, 35 1995, Application Serial No. 08/410,187 filed March 24, 1995, Application Serial No. 08/577,951 filed December 22, 1995 (now abandoned), Application Serial No. 08/615,760 filed March 13, 1996 (now abandoned), WO 97/23478 published July 3, 1997

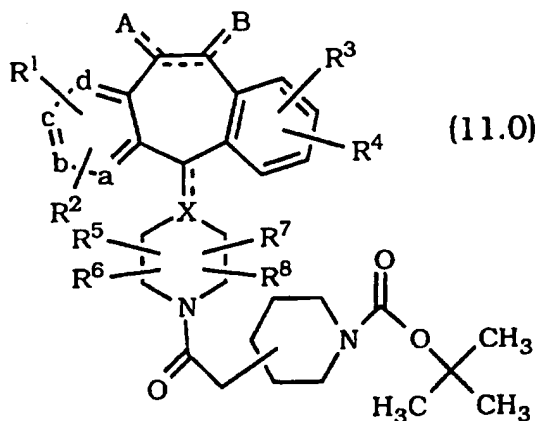
- 19 -

which discloses the subject matter of Serial No. 08/577,951 and 08/615,760, and Application Serial No. 08/713,323 filed September 13, 1996; the disclosures of each being incorporated herein by reference thereto; and according to the procedures described below.

Compounds of the invention can be prepared by reacting a compound of the formula:

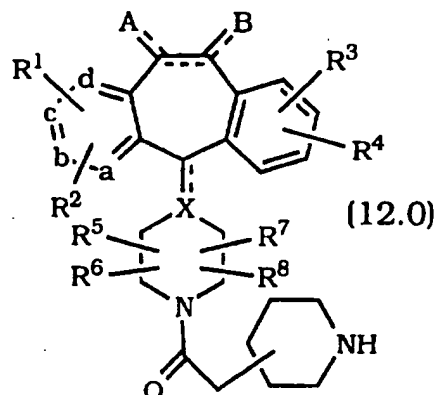


- wherein all substituents are as defined for Formula 1.0, with the appropriate protected piperidiny acetic acid (e.g., 1-N-t-butoxycarbonylpiperidiny acetic acid together with DEC/HOBT/NMM in DMF at about 25°C for about 18 hours to produce a compound of the formula:

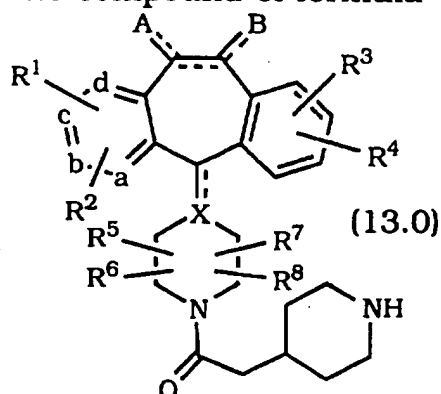


- The compound of Formula 11.0 is then reacted either with TFA or 10% sulfuric acid in dioxane and methanol followed by NaOH to produce the compound of Formula 12.0:

- 20 -

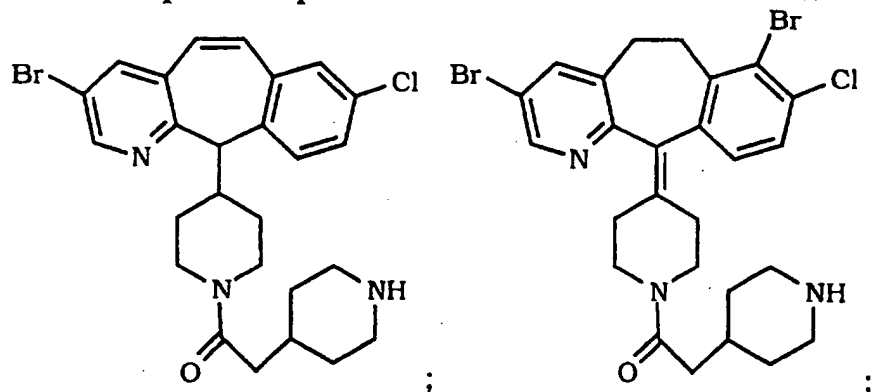


For example, the compound of formula

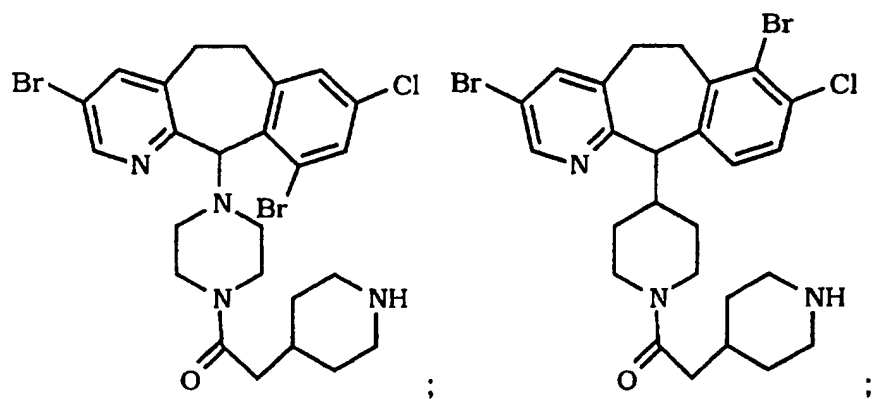
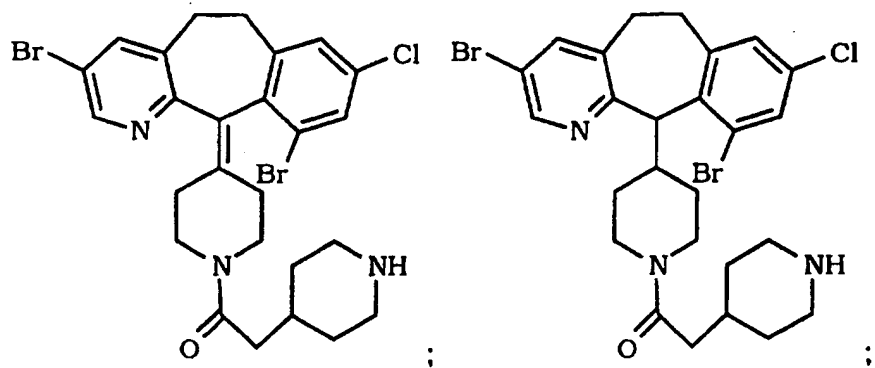
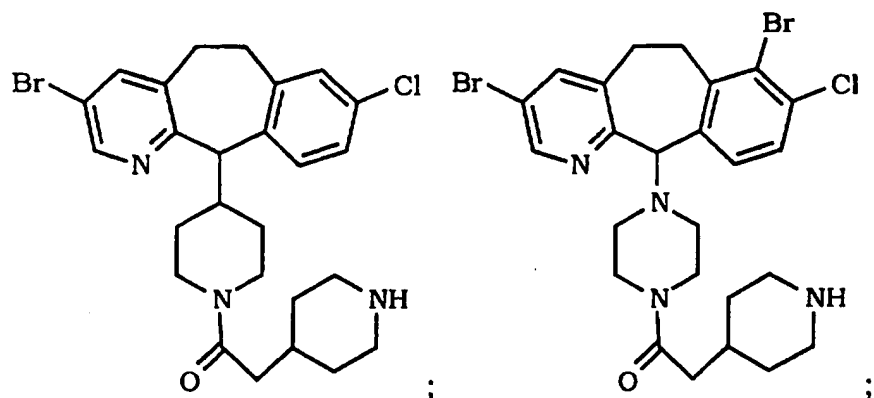


can be prepared by reaction of a compound of Formula 10.0 with
 5 1-N-t-butoxy-carbonylpiperidinyl-4-acetic acid as described
 above.

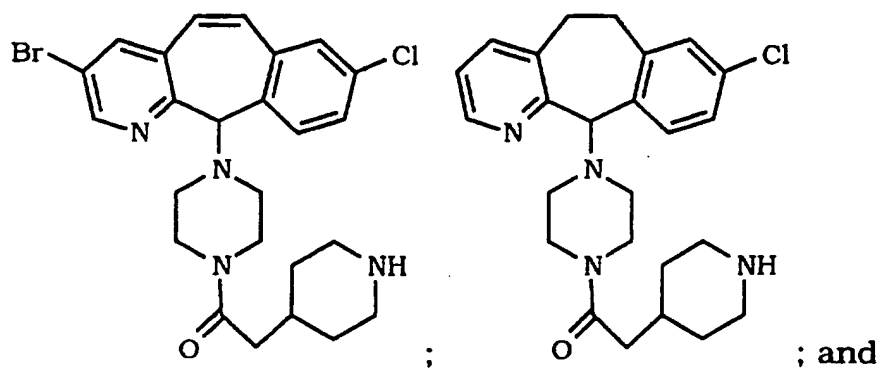
For Example, compounds of Formula 13.0 include:



- 21 -

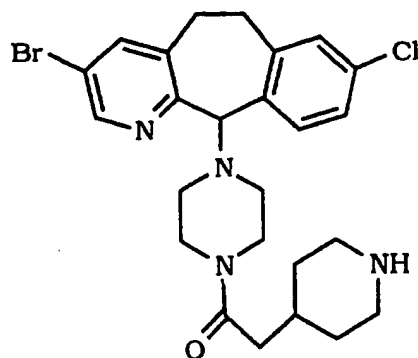


5



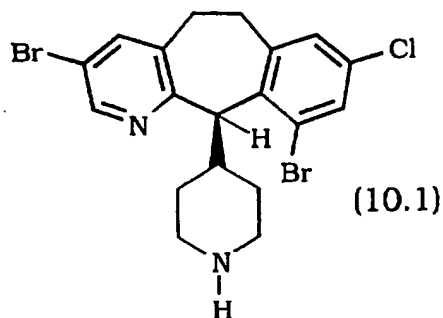
; and

- 22 -

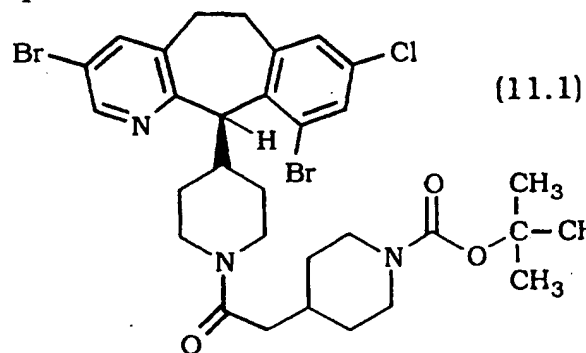


The preparation of these compounds are described in Preparative Examples 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 and 13, respectively, below.

- 5 The compounds of the invention can be prepared by reacting a compound of the formula:

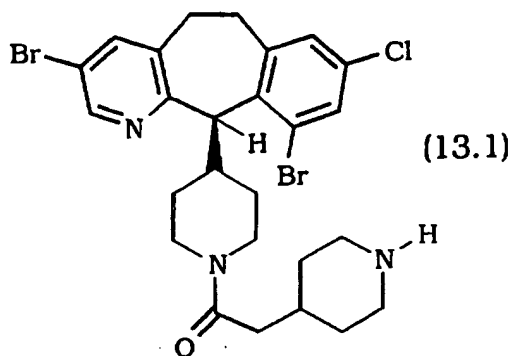


- with the appropriate protected piperidiny acetic acid (e.g., 1-N-t-butoxycarbonylpiperidiny acetic acid together with
 10 DEC/HOBT/NMM in DMF at about 25°C for about 18 hours to produce a compound of the formula:

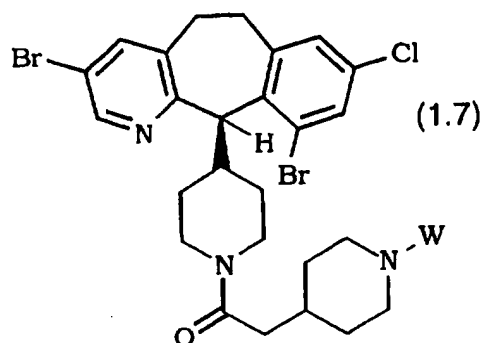


- The compound of Formula 11.1 is then reacted either with TFA
 or 10% sulfuric acid in dioxane and methanol followed by NaOH
 15 to produce the compound of Formula 13.1

- 23 -

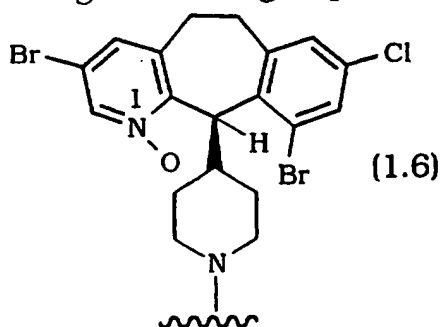


The amide compounds of this invention, represented by Formula 1.7

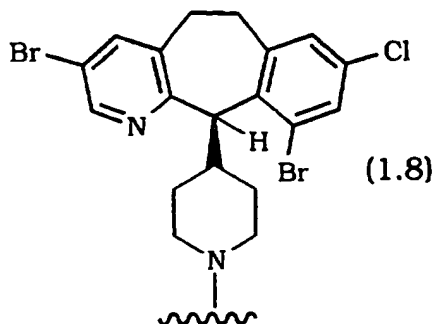


- 5 can be prepared by reacting the compound of Formula 13.1 with the appropriate carboxylic acid in the presence of a coupling agent such as DEC and HOBT in dimethylformamide. Alternatively, the compound of Formula 13.1 can be reacted with an acid chloride or anhydride in a solvent such as pyridine.

10 Compounds having an 1-N-O group:



can be prepared from the corresponding pyridyl compounds:

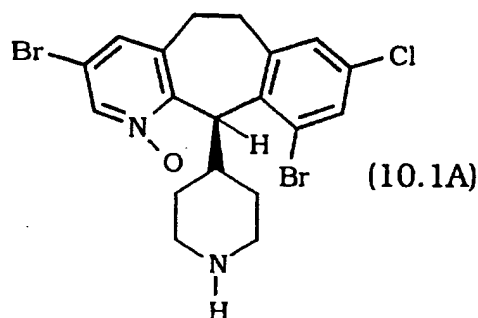


- 24 -

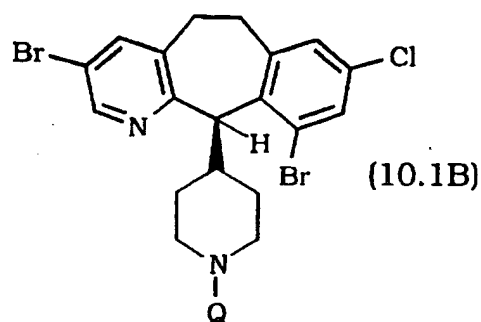
by oxidation with meta-chloroperoxybenzoic acid. This reaction is conducted in a suitable organic solvent, e.g., dichloromethane (usually anhydrous) or methylene chloride, at a suitable temperature, to produce the compounds of the invention having the N-O substituent at position 1 of Ring I of the tricyclic ring system.

Generally, the organic solvent solution of the starting tricyclic reactant is cooled to about 0°C before the m-chloroperoxybenzoic acid is added. The reaction is then allowed to warm to room temperature during the reaction period. The desired product can be recovered by standard separation means. For example, the reaction mixture can be washed with an aqueous solution of a suitable base, e.g., saturated sodium bicarbonate or NaOH (e.g., 1N NaOH), and then dried over anhydrous magnesium sulfate. The solution containing the product can be concentrated in vacuo. The product can be purified by standard means, e.g., by chromatography using silica gel (e.g., flash column chromatography).

Alternatively, N-O compounds can be made from intermediate:



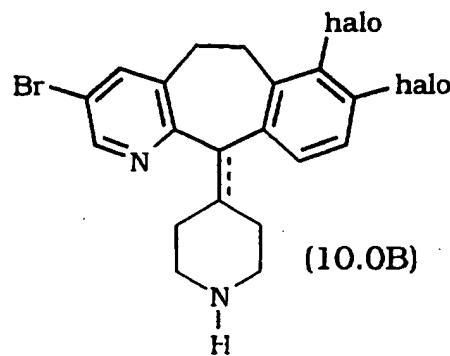
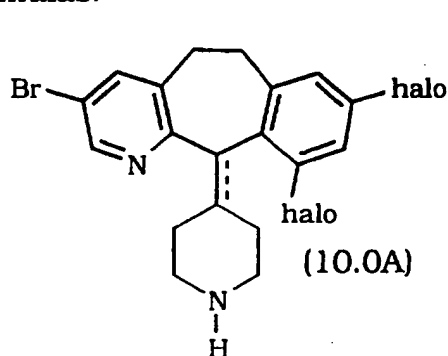
by the above oxidation procedure with m-chloroperoxybenzoic acid and



wherein Q is a protecting group, e.g., BOC. After oxidation the protecting group is removed by techniques well known in the art.

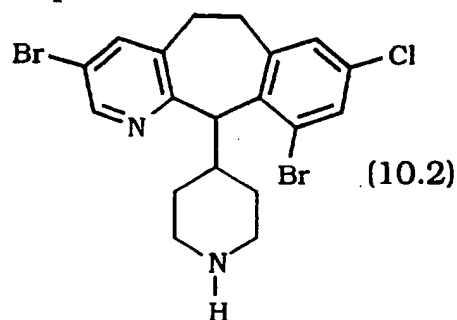
The N-O intermediate are then reacted further to produce the compounds of the invention.

Compounds of Formula 10.0 include the compounds of formulas:



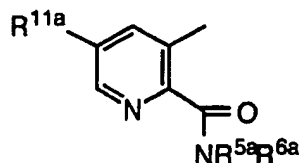
5

for example, the compound of formula



The compound of Formula 10.0A or 10.0B is prepared by methods known in the art, for example by methods disclosed in WO 95/10516, in U.S. 5,151,423 and those described below. The above intermediate compound can also be prepared by a procedure comprising the following steps:

(a) reacting an amide of the formula

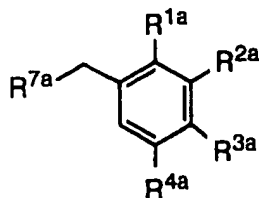


wherein R^{11a} is Br, R^{5a} is hydrogen and R^{6a} is C₁-C₆ alkyl, aryl or heteroaryl; R^{5a} is C₁-C₆ alkyl, aryl or heteroaryl and R^{6a} is hydrogen; R^{5a} and R^{6a} are independently selected from the group consisting of C₁-C₆ alkyl and aryl; or R^{5a} and R^{6a}, together with the nitrogen to which they are attached, form a ring comprising 4 to 6 carbon atoms or comprising 3 to 5 carbon atoms and one hetero moiety selected from the group consisting of -O- and -NR^{9a}-, wherein R^{9a} is H, C₁-C₆ alkyl or phenyl; with a compound of the formula

15

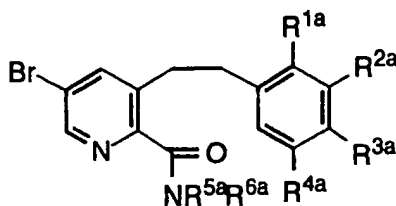
20

- 26 -



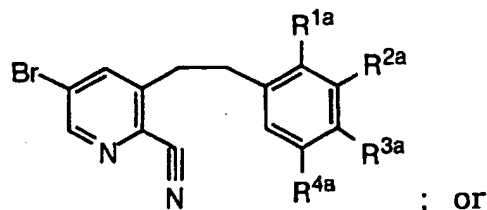
wherein R^{1a} , R^{2a} , R^{3a} and R^{4a} are independently selected from the group consisting of hydrogen and halo and R^{7a} is Cl or Br, in the presence of a strong base to obtain a compound of the

5 formula



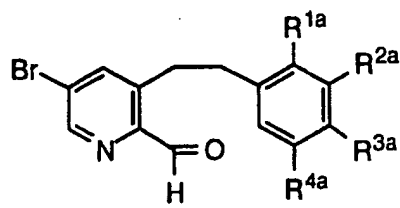
(b) reacting a compound of step (a) with

(i) POCl_3 to obtain a cyano compound of the formula



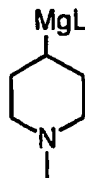
; or

(ii) DIBALH to obtain an aldehyde of the formula



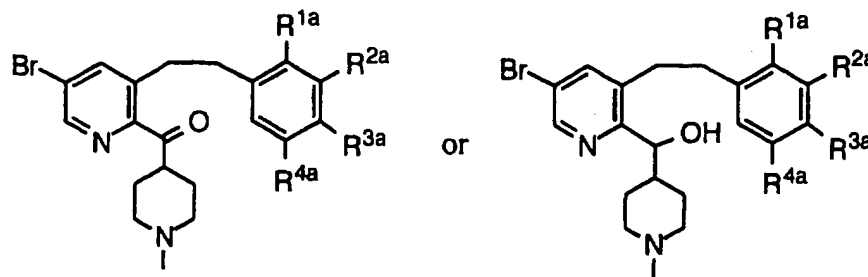
;

(c) reacting the cyano compound or the aldehyde with a piperidine derivative of the formula



15 wherein L is a leaving group selected from the group consisting of Cl and Br, to obtain a ketone or an alcohol of the formula below, respectively:

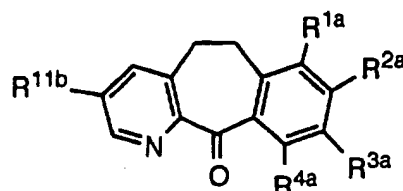
- 27 -



(d)(i) cyclizing the ketones with $\text{CF}_3\text{SO}_3\text{H}$ to obtain a compound of Formula 10.0A or 10.0B wherein the dotted line represents a double bond; or

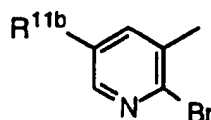
- 5 (d)(ii) cyclizing the alcohol with polyphosphoric acid to obtain an Intermediate compound wherein the dotted line represents a single bond.

Methods for preparing the Intermediate compounds disclosed in WO 95/10516, U.S. 5,151,423 and described below
 10 employ a tricyclic ketone intermediate. Such intermediates of the formula

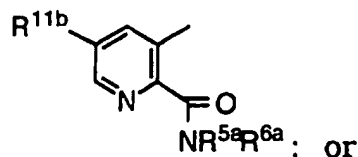


wherein R^{11b} , R^{1a} , R^{2a} , R^{3a} and R^{4a} are independently selected from the group consisting of hydrogen and halo, can be prepared
 15 by the following process comprising :

(a) reacting a compound of the formula



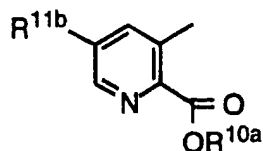
(i) with an amine of the formula $\text{NHR}^{5a}\text{R}^{6a}$, wherein R^{5a} and R^{6a} are as defined in the process above; in the presence
 20 of a palladium catalyst and carbon monoxide to obtain an amide of the formula:



(ii) with an alcohol of the formula R^{10a}OH , wherein R^{10a} is C_1 - C_6 lower alkyl or C_3 - C_6 cycloalkyl, in the presence of a

- 28 -

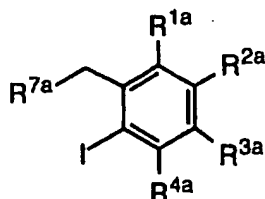
palladium catalyst and carbon monoxide to obtain the ester of the formula



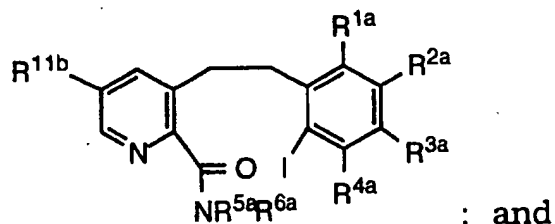
followed by reacting the ester with an amine of formula

5 $\text{NHR}^{5a}\text{R}^{6a}$ to obtain the amide;

(b) reacting the amide with an iodo-substituted benzyl compound of the formula

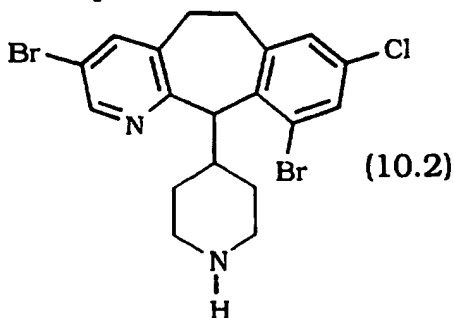


10 wherein R^{1a} , R^{2a} , R^{3a} , R^{4a} and R^{7a} are as defined above, in the presence of a strong base to obtain a compound of the formula



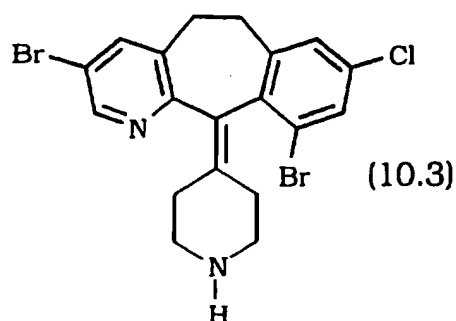
15 (c) cyclizing a compound of step (b) with a reagent of the formula R^{8a}MgL , wherein R^{8a} is $\text{C}_1\text{-C}_8$ alkyl, aryl or heteroaryl and L is Br or Cl, provided that prior to cyclization, compounds wherein R^{5a} or R^{6a} is hydrogen are reacted with a suitable N-protecting group.

(+)-Isomers of compounds of Formula 10.2



20 can be prepared with high enantioselectivity by using a process comprising enzyme catalyzed transesterification. Preferably, a racemic compound of Formula 10.3

- 29 -



is reacted with an enzyme such as Toyobo LIP-300 and an acylating agent such as trifluoroethyl isobutyrate; the resultant (+)-amide is then isolated from the (-)-enantiomeric amine by techniques well known in the art, and then the (+)-amide is hydrolyzed, for example by refluxing with an acid such as H₂SO₄, and the resulting compound is then reduced with DIBAL by techniques well known in the art to obtain the corresponding optically enriched (+)-isomer of Formula 10.2. Alternatively, a racemic compound of Formula 10.3, is first reduced to the corresponding racemic compound of Formula 10.2 and then treated with the enzyme (Toyobo LIP-300) and acylating agent as described above to obtain the (+)-amide, which is hydrolyzed to obtain the optically enriched (+)-isomer.

Those skilled in the art will appreciate that compounds of Formula 1.0 having other R¹, R², R³ and R⁴ substituents may be made by the above enzyme process.

To produce the compounds of Formula 1.0, the compounds of Formula 12.0 or 13.0 are reacted with the appropriate halo substituted heteroaryl, heterocycloalkyl or cycloalkyl group in a suitable organic solvent with a suitable base to add the appropriate W group. These condensation reactions are conducted according to procedures well known in the art.

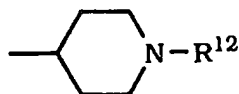
For example, the compounds of Formulas 12.0 or 13.0 are reacted with the appropriate halo-heteroaryl (e.g., Br-heteroaryl or Cl-heteroaryl) in a suitable organic solvent (e.g., dimethylformamide) with a suitable base (e.g., sodium bicarbonate) to produce compounds of formula 1.0 wherein W is heteroaryl.

Also, for example, the compounds of Formula 12.0 or 13.0 are reacted with the appropriate halo-heterocycloalkyl or halocycloalkyl (e.g., Br-heterocycloalkyl or Br-cycloalkyl) in a suitable organic solvent (e.g., dimethylformamide) with a suitable base

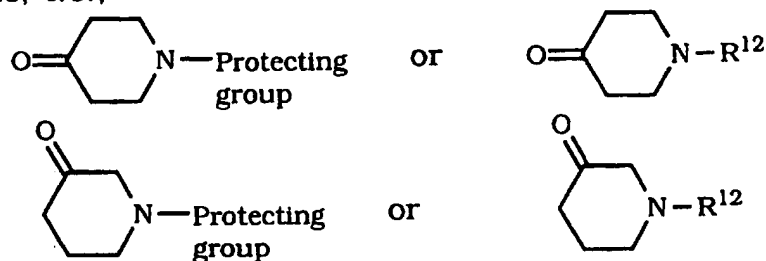
- 30 -

(e.g., NaH) to produce compounds of formula 1.0 wherein W is heterocycloalkyl.

Compounds of Formula 1.0 wherein W is



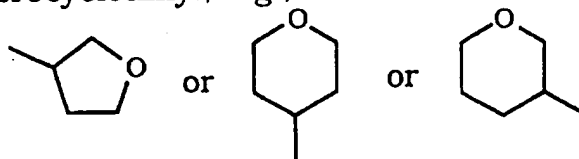
- 5 can be prepared by procedures well known in the art. For example, a compound of Formula 12.0 or 13.0 can be condensed with a suitably protected (when R¹² is H) or substituted 3- or 4-piperidone, i.e.,



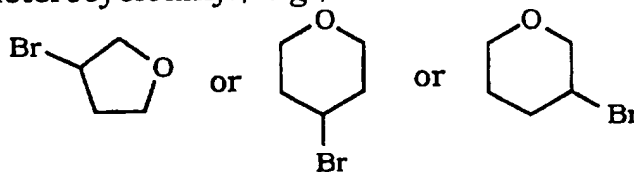
10

using TiCl₄ and reducing the intermediate with NaCNBH₄.

Compounds of Formula 1.0 wherein W is an oxygen containing heterocycloalkyl, e.g.,



- 15 can be prepared by procedures well known in the art by the alkylation of a compound of Formula 12.0 or 13.0 with the halo-substituted heterocycloalkyl, e.g.,

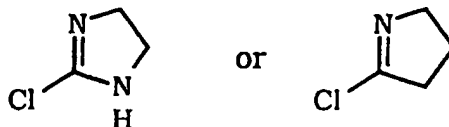


- 20 in the presence of a suitable base (e.g., NaH) and a suitable solvent (e.g., THF).

Also, for example, the compounds of Formula 12.0 or 13.0 are reacted with the appropriate halo-cyclic guanidine or halo-cyclic amidine in a suitable solvent (e.g., DMF) with a suitable base (e.g., Na₂CO₃) to produce compounds wherein W is a cyclic

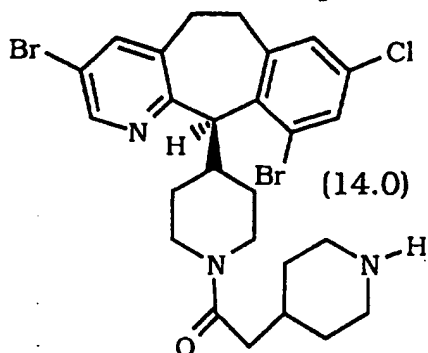
25 guanidine or cyclic amidine. For example, reaction of the compound of Formula 14.0 (below) with

- 31 -

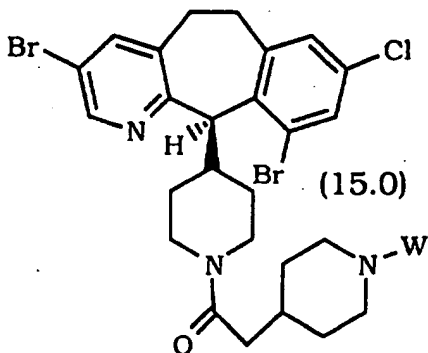


- [prepared as described in "The Chemistry of the Carbon-Nitrogen Double Bond," Saul Patai, Ed., Chapter 13, pp. 597-662, John Wiley & Sons (1970) in DMF with Na₂CO₃ gives the compounds of
- 5 Formula 9.1 or 9.2, respectively.

For example, reaction of the compound of the formula



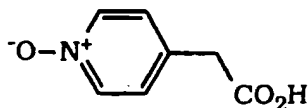
- with the above mentioned halo substituted heteroaryl, heterocycloalkyl or cycloalkyl groups yields a compound of the
- 10 formula:



wherein W is as defined for Formula 1.0.

- Compounds of the invention are exemplified by the
- 15 following examples, which should not be construed to limit the scope of the disclosure.

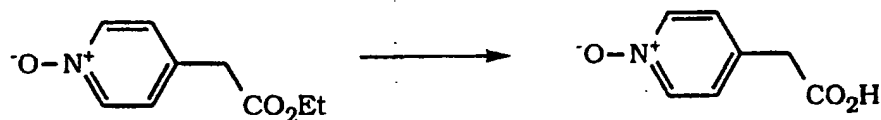
PREPARATIVE EXAMPLE 1



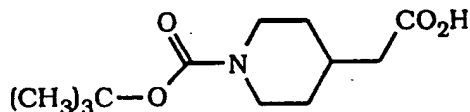
- 32 -

Step A:

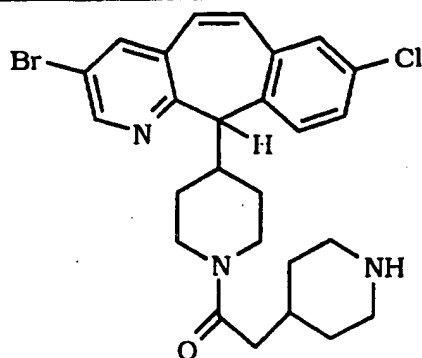
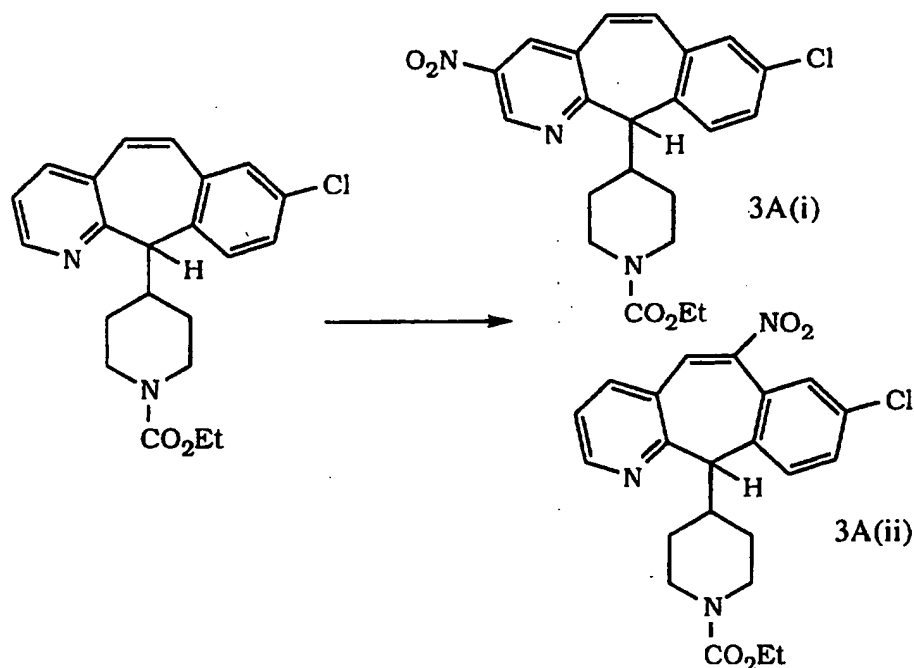
- Combine 10 g (60.5 mmol) of ethyl 4-pyridylacetate and 120 mL of dry CH₂Cl₂ at -20°C, add 10.45 g (60.5 mmol) of MCPBA and stir at -20°C for 1 hour and then at 25°C for 67 hours. Add an additional 3.48 g (20.2 mmoles) of MCPBA and stir at 25°C for 24 hours. Dilute with CH₂Cl₂ and wash with saturated NaHCO₃ (aqueous) and then water. Dry over MgSO₄, concentrate in vacuo to a residue, and chromatograph (silica gel, 2%-5.5% (10% NH₄OH in MeOH)/CH₂Cl₂) to give 8.12 g of the product compound. Mass Spec.: MH⁺ = 182.15.

Step B:

- Combine 3.5 g (19.3 mmol) of the product of Step A, 17.5 mL of EtOH and 96.6 mL of 10% NaOH (aqueous) and heat the mixture at 67°C for 2 hours. Add 2 N HCl (aqueous) to adjust to pH = 2.37 and concentrate in vacuo to a residue. Add 200 mL of dry EtOH, filter through celite® and wash the filter cake with dry EtOH (2X50 ml). Concentrate the combined filtrates in vacuo to give 2.43 g of the title compound.

PREPARATIVE EXAMPLE 2

- The title compound is prepared via the process disclosed in PCT International Publication No. WO95/10516.

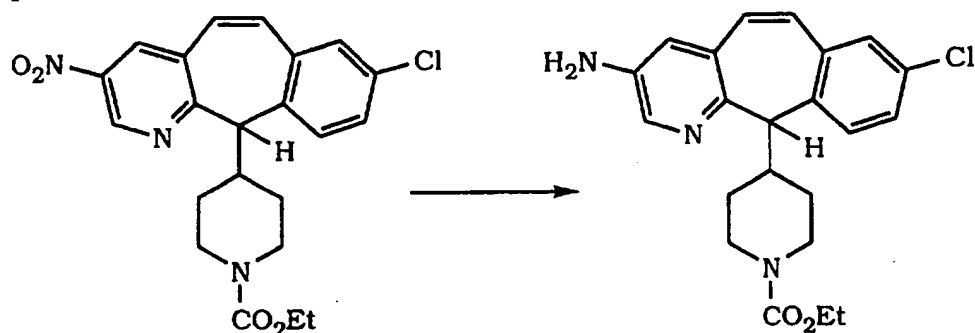
PREPARATIVE EXAMPLE 3Step A:

- 5 Combine 14.95 g (39 mmol) of 8-chloro-11-(1-ethoxy-carbonyl-4-piperidinyl)-11H-benzo[5,6]cyclohepta[1,2-b]pyridine and 150 mL of CH₂Cl₂, then add 13.07 g (42.9 mmol) of (nBu)₄NNO₃ and cool the mixture to 0°C. Slowly add (dropwise) a
- 10 solution of 6.09 mL (42.9 mmol) of TFAA in 20 mL of CH₂Cl₂ over 1.5 hours. Keep the mixture at 0°C overnight, then wash successively with saturated NaHCO₃ (aqueous), water and brine. Dry the organic solution over Na₂SO₄, concentrate in vacuo to a residue and chromatograph the residue (silica gel, EtOAc/hexane gradient) to give 4.32 g and 1.90 g of the two product compounds
- 15 3A(i) and 3A(ii), respectively.

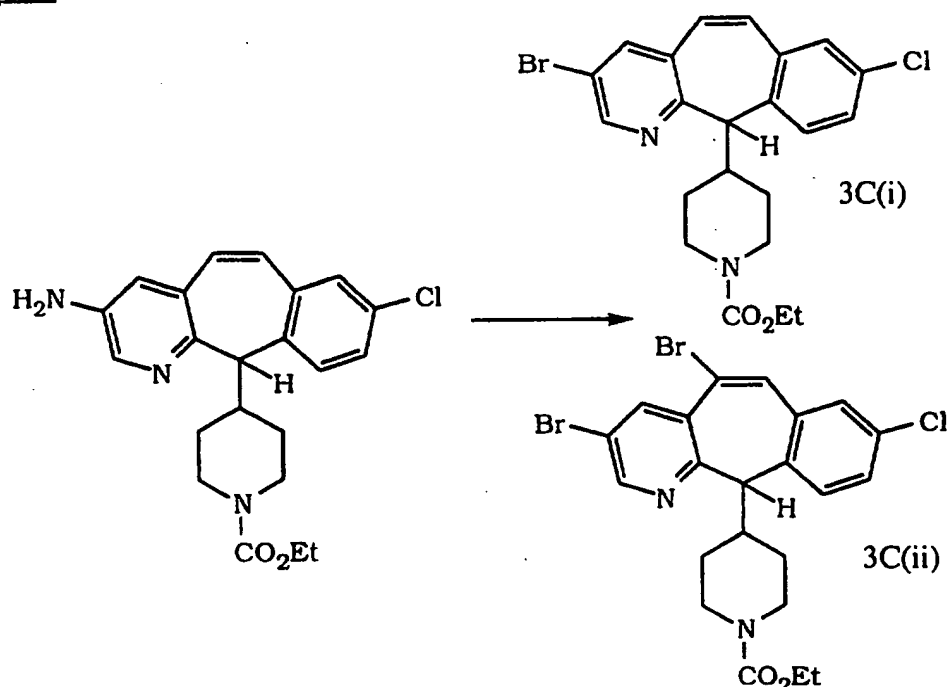
Mass Spec. for compound 3A(i): MH⁺ = 428.2;

Mass Spec. for compound 3A(ii): MH⁺ = 428.3.

- 34 -

Step B:

Combine 22.0 g (51.4 mmol) of the product 3A(i) from Step A, 150 mL of 85% EtOH (aqueous), 25.85 g (0.463 mole) of Fe powder and 2.42 g (21.8 mmol) of CaCl_2 , and heat at reflux overnight. Add 12.4 g (0.222 mole) of Fe powder and 1.2 g (10.8 mmol) of CaCl_2 and heat at reflux for 2 hours. Add another 12.4 g (0.222 mole) of Fe powder and 1.2 g (10.8 mmol) of CaCl_2 and heat at reflux for 2 hours more. Filter the hot mixture through celite®, wash the celite® with 50 mL of hot EtOH and concentrate the filtrate in vacuo to a residue. Add 100 mL of anhydrous EtOH, concentrate to a residue and chromatograph the residue (silica gel, MeOH/ CH_2Cl_2 gradient) to give 16.47 g of the product compound.

15 Step C:

Combine 16.47 g (41.4 mmol) of the product from Step B, and 150 mL of 48% HBr (aqueous) and cool to -3°C . Slowly add

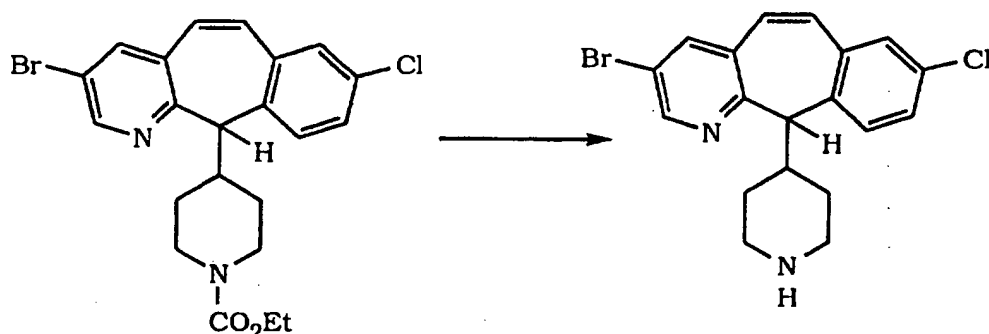
- 35 -

(dropwise) 18 mL of bromine, then slowly add (dropwise) a solution of 8.55 g (0.124 mole) of NaNO_2 in 85 mL of water. Stir for 45 minutes at -3° to 0°C , then adjust to $\text{pH} = 10$ by adding 50% NaOH (aqueous). Extract with EtOAc , wash the extracts with brine and dry the extracts over Na_2SO_4 . Concentrate to a residue and chromatograph (silica gel, EtOAc /hexane gradient) to give 10.6 g and 3.28 g of the two product compounds 3C(i) and 3C(ii), respectively.

Mass Spec. for compound 3C(i): $\text{MH}^+ = 461.2$;

Mass Spec. for compound 3C(ii): $\text{MH}^+ = 539$.

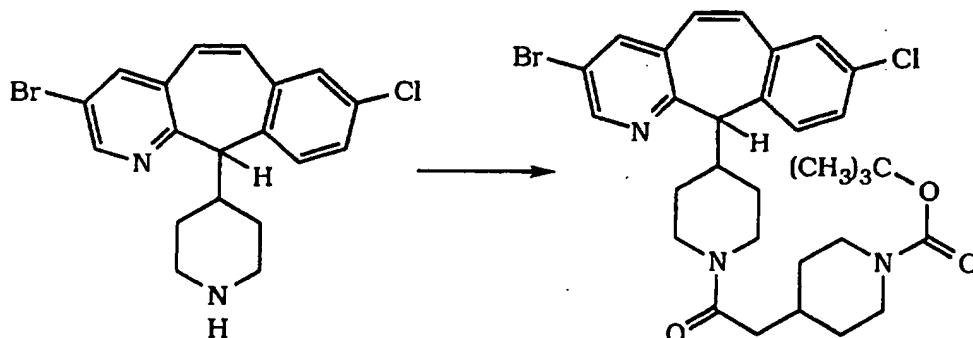
Step D:



Hydrolyze the product 3C(i) of Step C by dissolving in concentrated HCl and heating to about 100°C for @ 16 hours. Cool the mixture, the neutralize with 1 M NaOH (aqueous). Extract with CH_2Cl_2 , dry the extracts over MgSO_4 , filter and concentrate in vacuo to the title compound.

Mass Spec.: $\text{MH}^+ = 466.9$.

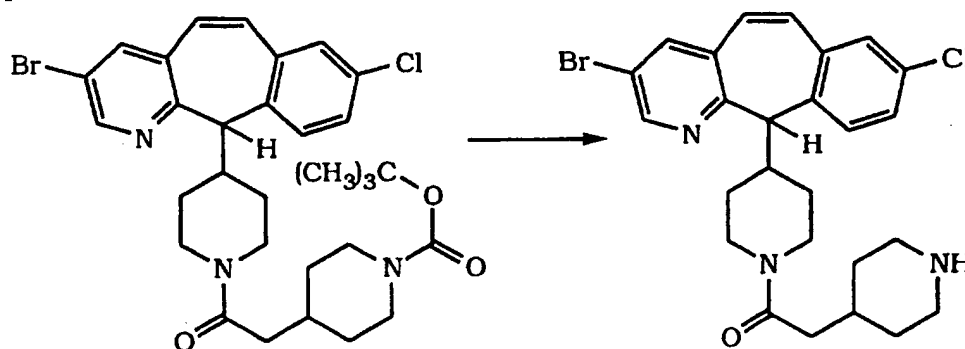
Step E:



Dissolve 1.160 g (2.98 mmol) of the title compound from Step D in 20 mL of DMF , stir at room temperature, and add 0.3914 g (3.87 mmol) of 4-methyl-morpholine, 0.7418 g (3.87 mmol) of DEC, 0.5229 g (3.87 mmol) of HOBT , and 0.8795 g (3.87 mmol) of 1-N-*t*-butoxycarbonyl-piperidinyl-4-acetic acid.

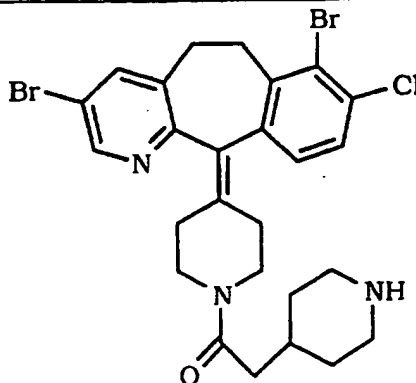
- 36 -

- Stir the mixture at room temperature for 2 days, then concentrate in vacuo to a residue and partition the residue between CH_2Cl_2 and water. Wash the organic phase successively with saturated NaHCO_3 (aqueous), 10% NaH_2PO_4 (aqueous) and
- 5 brine. Dry the organic phase over MgSO_4 , filter and concentrate in vacuo to a residue. Chromatograph the residue (silica gel, 2% $\text{MeOH}/\text{CH}_2\text{Cl}_2 + \text{NH}_3$) to give 1.72 g of the product. m.p. = 94.0-94.5°C, Mass Spec.: $\text{MH}^+ = 616.3$,
elemental analysis: calculated - C, 60.54; H, 6.06; N, 6.83
10 found - C, 59.93; H, 6.62; N, 7.45.

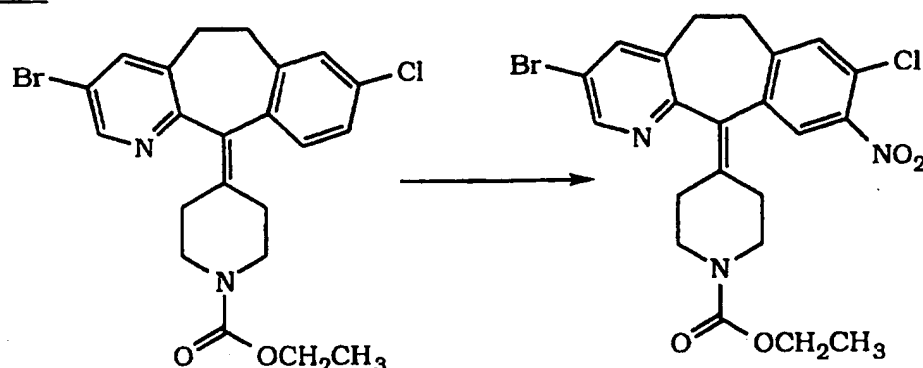
Step F:

- Combine 1.67 g (2.7 mmol) of the product of Step E and 20 mL of CH_2Cl_2 and stir at 0°C. Add 20 mL of TFA, stir the mixture
- 15 for 2 hours, then basify the mixture with 1 N NaOH (aqueous). Extract with CH_2Cl_2 , dry the organic phase over MgSO_4 , filter and concentrate in vacuo to give 1.16 g of the product. m.p. = 140.2-140.8°C, Mass Spec.: $\text{MH}^+ = 516.2$.

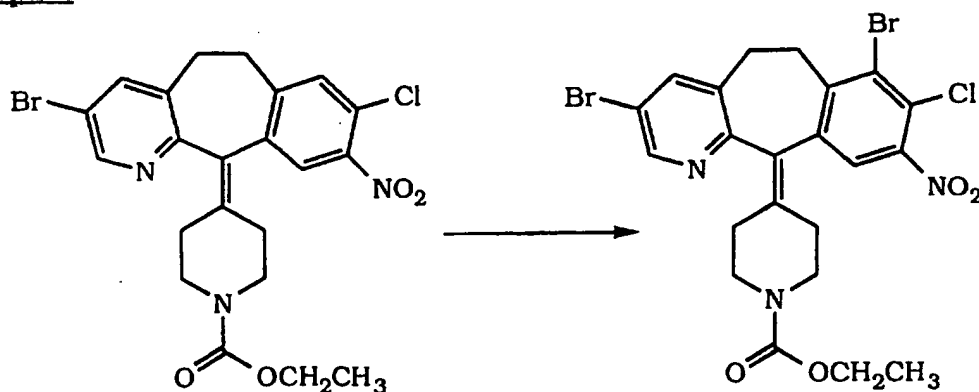
20

PREPARATIVE EXAMPLE 4

- 37 -

Step A:

- Combine 25.86 g (55.9 mmol) of 4-(8-chloro-3-bromo-5,6-dihydro-1H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)-1-piperidine-1-carboxylic acid ethyl ester and 250 mL of concentrated H_2SO_4 at -5°C , then add 4.8 g (56.4 mmol) of NaNO_3 and stir for 2 hours. Pour the mixture into 600 g of ice and basify with concentrated NH_4OH (aqueous). Filter the mixture, wash with 300 mL of water, then extract with 500 mL of CH_2Cl_2 . Wash the extract with 200 mL of water, dry over MgSO_4 , then filter and concentrate in vacuo to a residue. Chromatograph the residue (silica gel, 10% EtOAc/ CH_2Cl_2) to give 24.4 g (86% yield) of the product. m.p. = $165-167^\circ\text{C}$, Mass Spec.: $\text{MH}^+ = 506$ (Cl),
- 15 elemental analysis: calculated - C, 52.13; H, 4.17; N, 8.29
 found - C, 52.18; H, 4.51; N, 8.16.

Step B:

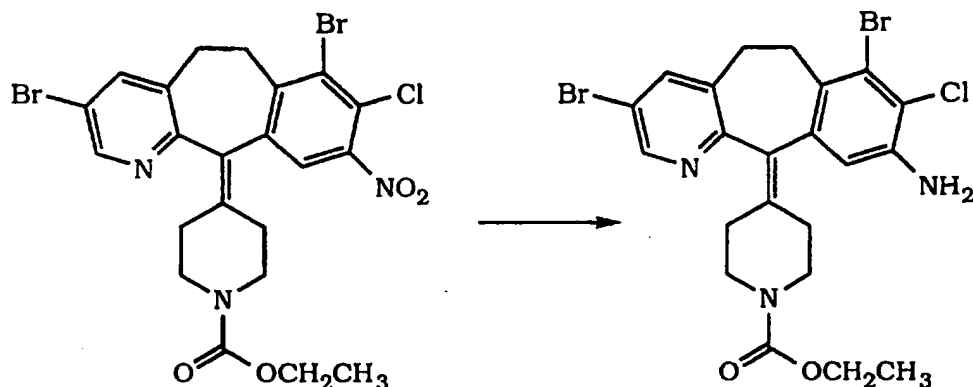
- Combine 20 g (40.5 mmol) of the product of Step A and 200 mL of concentrated H_2SO_4 at 20°C , then cool the mixture to 0°C . Add 7.12 g (24.89 mmol) of 1,3-dibromo-5,5-dimethylhydantoin to the mixture and stir for 3 hours at 20°C . Cool to 0°C , add an additional 1.0 g (3.5 mmol) of the dibromohydantoin and stir at 20°C for 2 hours. Pour the mixture into 400 g of ice,

basify with concentrated NH_4OH (aqueous) at 0°C , and collect the resulting solid by filtration. Wash the solid with 300 mL of water, slurry in 200 mL of acetone and filter to provide 19.79 g (85.6% yield) of the product. m.p. = $236\text{--}237^\circ\text{C}$, Mass Spec.: $\text{MH}^+ = 584$

5 (CI).

elemental analysis: calculated - C, 45.11; H, 3.44; N, 7.17
found - C, 44.95; H, 3.57; N, 7.16.

Step C:



Combine 25 g (447 mmol) of Fe filings, 10 g (90 mmol) of CaCl₂ and a suspension of 20 g (34.19 mmol) of the product of Step B in 700 mL of 90:10 EtOH/water at 50°C. Heat the mixture at reflux overnight, filter through Celite® and wash the filter cake with 2 X 200 mL of hot EtOH. Combine the filtrate and washes,

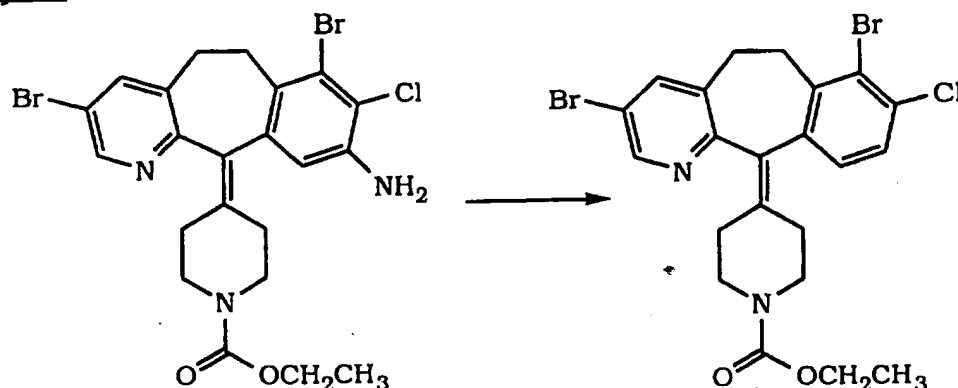
and concentrate in vacuo to a residue. Extract the residue with 600 mL of CH₂Cl₂, wash with 300 mL of water and dry over MgSO₄. Filter and concentrate in vacuo to a residue, then chromatograph (silica gel, 30% EtOAc/CH₂Cl₂) to give 11.4 g (60% yield) of the product. m.p. = 211-212°C,

Mass Spec.: MH⁺ = 554 (CI),

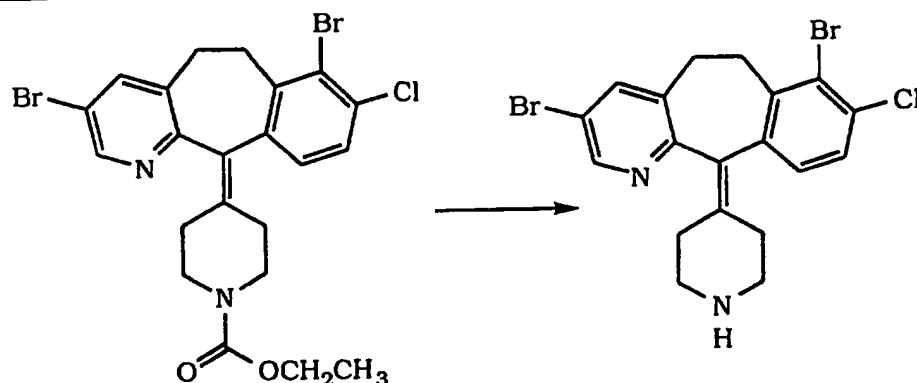
elemental analysis:

calculated - C, 47.55; H, 3.99; N, 7.56
found - C, 47.45; H, 4.31; N, 7.49.

- 39 -

Step D:

Slowly add (in portions) 20 g (35.9 mmol) of the product of Step C to a solution of 8 g (116 mmol) of NaNO₂ in 120 mL of concentrated HCl (aqueous) at -10°C. Stir the resulting mixture at 0°C for 2 hours, then slowly add (dropwise) 150 mL (1.44 mole) of 50% H₃PO₂ at 0°C over a 1 hour period. Stir at 0°C for 3 hours, then pour into 600 g of ice and basify with concentrated NH₄OH (aqueous). Extract with 2 X 300 mL of CH₂Cl₂, dry the extracts over MgSO₄, then filter and concentrate in vacuo to a residue. Chromatograph the residue (silica gel, 25% EtOAc/hexanes) to give 13.67 g (70% yield) of the product. m.p. = 163-165°C, Mass Spec.: MH⁺ = 539 (CI), elemental analysis: calculated - C, 48.97; H, 4.05; N, 5.22 found - C, 48.86; H, 3.91; N, 5.18.

Step E:

Combine 6.8 g (12.59 mmol) of the product of Step D and 100 mL of concentrated HCl (aqueous) and stir at 85°C overnight. Cool the mixture, pour it into 300 g of ice and basify with concentrated NH₄OH (aqueous). Extract with 2 x 300 mL of CH₂Cl₂, then dry the extracts over MgSO₄. Filter, concentrate in vacuo to a residue, then chromatograph (silica gel, 10%

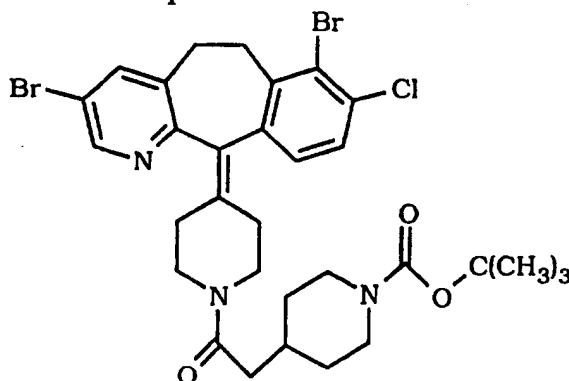
- 40 -

MeOH/EtOAc + 2% NH₄OH (aqueous)) to give 5.4 g (92% yield) of the title compound. m.p. = 172-174°C, Mass Spec.: MH⁺ = 467 (FAB),

elemental analysis: calculated - C, 48.69; H, 3.65; N, 5.97
found - C, 48.83; H, 3.80; N, 5.97.

Step F:

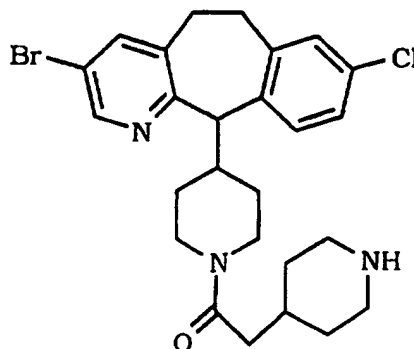
Following essentially the same procedure as Step C of Preparative Example 5 below, the title compound from Step E above is reacted with 1-N-t-butoxycarbonylpiperidiny-4-acetic acid to produce the compound



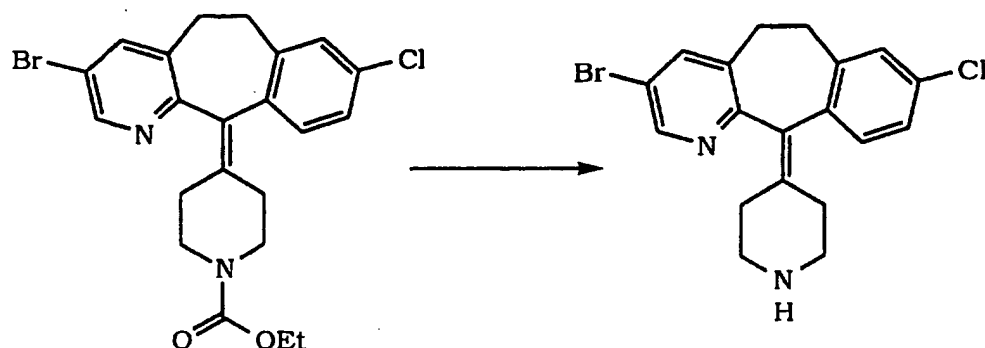
Step G:

Following essentially the same procedure as Step D of Preparative Example 5 below, the title compound from Step F above is deprotected to yield the title compound of Preparative Example 4.

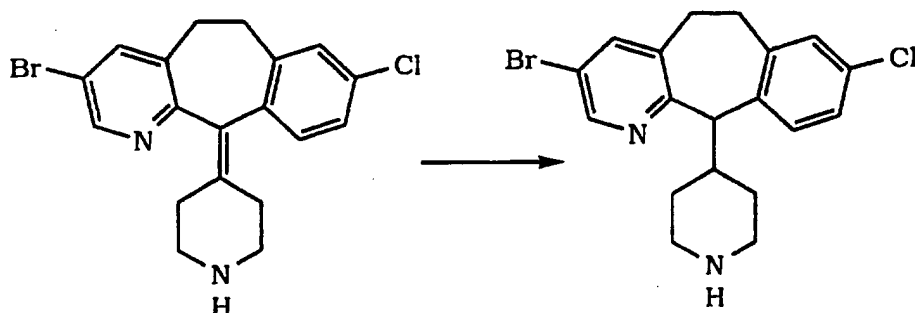
PREPARATIVE EXAMPLE 5



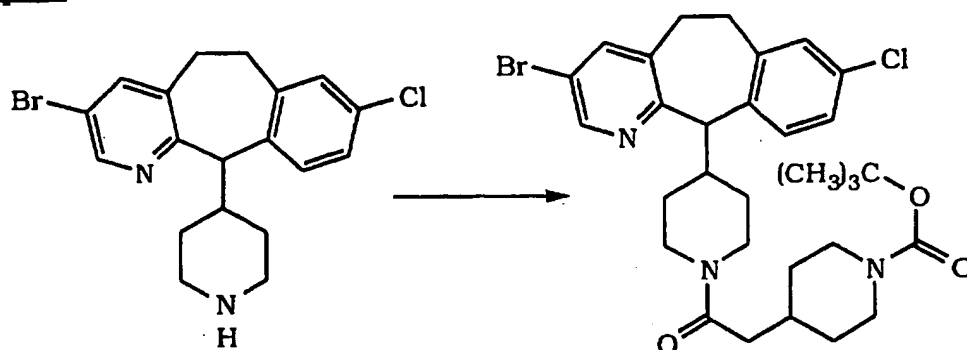
- 41 -

Step A:

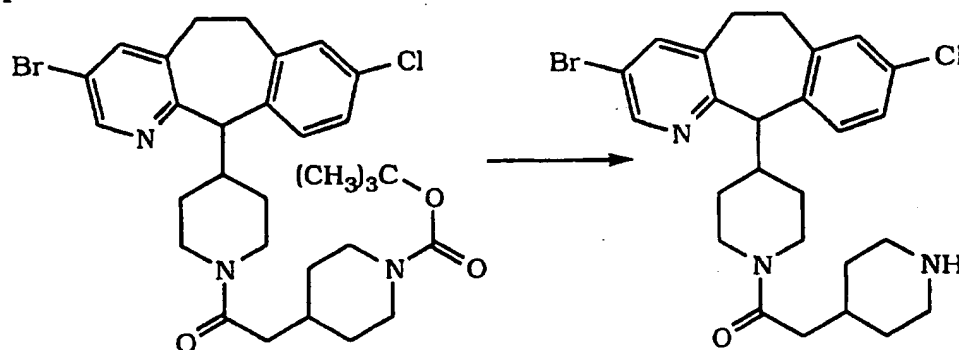
- Hydrolyze 2.42 g of 4-(8-chloro-3-bromo-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)-1-piperidine-1-carboxylic acid ethyl ester via substantially the same procedure as described in Preparative Example 3, Step D, to give 1.39 g (69% yield) of the product.

Step B:

- Combine 1 g (2.48 mmol) of the product of Step A and 25 mL of dry toluene, add 2.5 mL of 1 M DIBAL in toluene and heat the mixture at reflux. After 0.5 hours, add another 2.5 mL of 1 M DIBAL in toluene and heat at reflux for 1 hour. (The reaction is monitored by TLC using 50% MeOH/CH₂Cl₂ + NH₄OH (aqueous).)
- Cool the mixture to room temperature, add 50 mL of 1 N HCl (aqueous) and stir for 5 min. Add 100 mL of 1 N NaOH (aqueous), then extract with EtOAc (3 X 150 mL). Dry the extracts over MgSO₄, filter and concentrate *in vacuo* to give 1.1 g of the title compound.

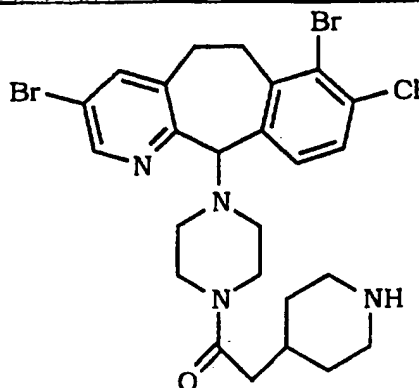
Step C:

- Combine 0.501 g (1.28 mmol) of the title compound of Step B and 20 mL of dry DMF, then add 0.405 g (1.664 mmol) of 1-N-t-butoxycarbonylpiperidiny-4-acetic acid, 0.319 g (1.664 mmol) of DEC, 0.225 g (1.664 mmol) of HOBT, and 0.168 g (1.664 mmol) of 4-methylmorpholine and stir the mixture at room temperature overnight. Concentrate the mixture *in vacuo* to a residue, then partition the residue between 150 mL of CH₂Cl₂ and 150 mL of saturated NaHCO₃ (aqueous). Extract the aqueous phase with another 150 mL of CH₂Cl₂. Dry the organic phase over MgSO₄, and concentrate *in vacuo* to a residue. Chromatograph the residue (silica gel, 500 mL hexane, 1 L of 1% MeOH/CH₂Cl₂ + 0.1% NH₄OH (aqueous), then 1 L of 2% MeOH/CH₂Cl₂ + 0.1% NH₄OH (aqueous)) to give 0.575 g of the product. m.p. = 115°-125°C; Mass Spec.: MH⁺ = 616.

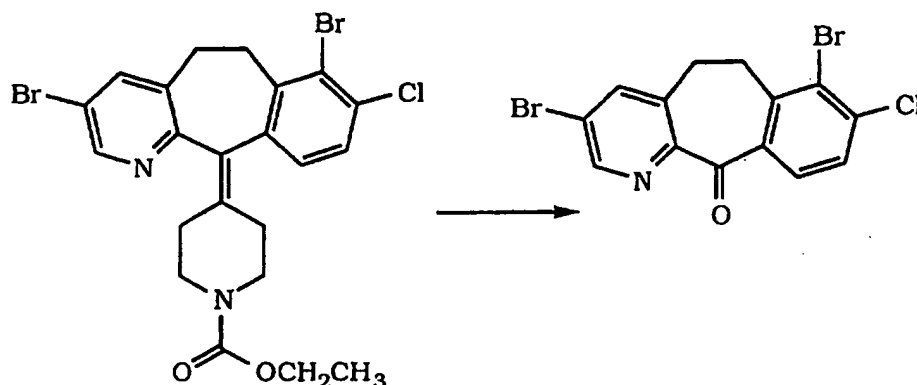
Step D:

- Combine 0.555 g (0.9 mmol) of the product of Step C and 15 mL of CH₂Cl₂ and cool the mixture to 0°C. Add 15 mL of TFA and stir at 0°C for 2 hours. Concentrate *in vacuo* at 40-45°C to a residue, then partition the residue between 150 mL of CH₂Cl₂ and 100 mL of saturated NaHCO₃ (aqueous). Extract the aqueous layer with 100 mL of CH₂Cl₂, combine the extracts and dry over MgSO₄. Concentrate *in vacuo* to give 0.47 g of the product.

- 43 -

m.p. = 140°-150°C; Mass Spec.: $MH^+ = 516$.PREPARATIVE EXAMPLE 6

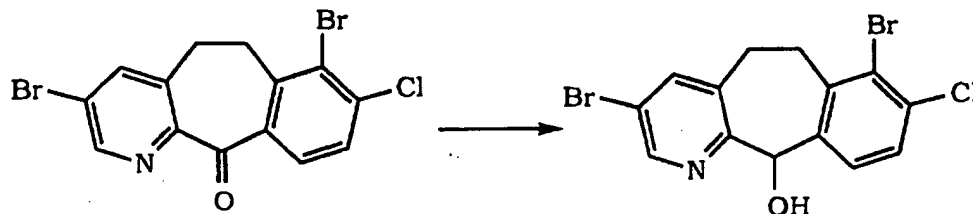
5 [racemic as well as (+)- and (-)-isomers]

Step A:

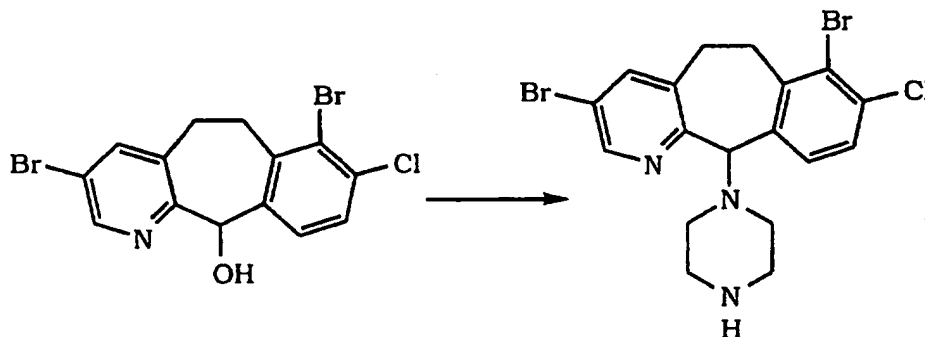
Combine 16.6 g (0.03 mole) of the product of Preparative Example 4, Step D, with a 3:1 solution of CH_3CN and water
 10 (212.65 mL CH_3CN and 70.8 mL of water) and stir the resulting slurry overnight at room temperature. Add 32.833 g (0.153 mole) of $NaIO_4$ and then 0.31 g (2.30 mmol) of RuO_2 and stir at room temperature give 1.39 g (69% yield) of the product. (The addition of RuO is accompanied by an exothermic reaction and
 15 the temperature climbs from 20° to 30°C.) Stir the mixture for 1.3 hrs. (temperature returned to 25°C after about 30 min.), then filter to remove the solids and wash the solids with CH_2Cl_2 . Concentrate the filtrate *in vacuo* to a residue and dissolve the residue in CH_2Cl_2 . Filter to remove insoluble solids and wash the
 20 solids with CH_2Cl_2 . Wash the filtrate with water, concentrate to a volume of about 200 mL and wash with bleach, then with water. Extract with 6 N HCl (aqueous). Cool the aqueous extract to 0°C and slowly add 50% NaOH (aqueous) to adjust to pH = 4 while

- 44 -

keeping the temperature $<30^{\circ}\text{C}$. Extract twice with CH_2Cl_2 , dry over MgSO_4 and concentrate *in vacuo* to a residue. Slurry the residue in 20 mL of EtOH and cool to 0°C . Collect the resulting solids by filtration and dry the solids *in vacuo* to give 7.95 g of the product. ^1H NMR (CDCl_3 , 200 MHz): 8.7 (s, 1H); 7.85 (m, 6H); 7.5 (d, 2H); 3.45 (m, 2H); 3.15 (m, 2H).

Step B:

Combine 21.58 g (53.75 mmol) of the product of Step A and 500 mL of an anhydrous 1:1 mixture of EtOH and toluene, add 1.43 g (37.8 mmol) of NaBH_4 and heat the mixture at reflux for 10 min. Cool the mixture to 0°C , add 100 mL of water, then adjust to $\text{pH} \approx 4-5$ with 1 M HCl (aqueous) while keeping the temperature $<10^{\circ}\text{C}$. Add 250 mL of EtOAc and separate the layers. Wash the organic layer with brine (3 X 50 mL) then dry over Na_2SO_4 . Concentrate *in vacuo* to a residue (24.01 g) and chromatograph the residue (silica gel, 30 % hexane/ CH_2Cl_2) to give the product. Impure fractions were purified by rechromatography. A total of 18.57 g of the product was obtained. ^1H NMR ($\text{DMSO}-d_6$, 400 MHz): 8.5 (s, 1H); 7.9 (s, 1H); 7.5 (d of d, 2H); 6.2 (s, 1H); 6.1 (s, 1H); 3.5 (m, 1H); 3.4 (m, 1H); 3.2 (m, 2H).

Step C:

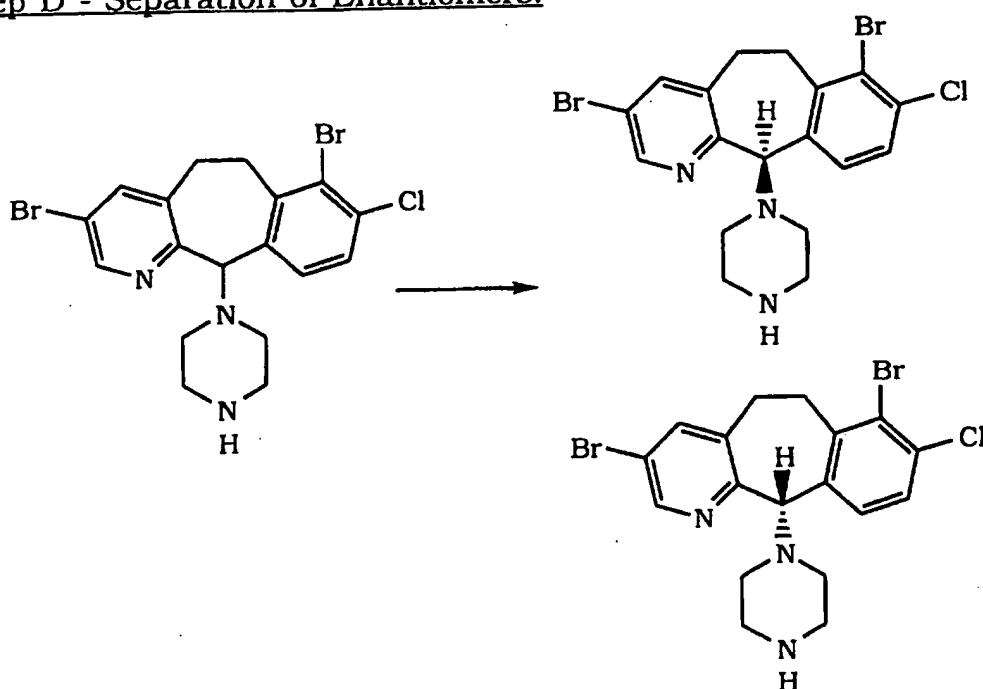
Combine 18.57 g (46.02 mmol) of the product of Step B and 500 mL of CHCl_3 , then add 6.70 mL (91.2 mmol) of SOCl_2 , and stir the mixture at room temperature for 4 hrs. Add a solution of 35.6 g (0.413 mole) of piperazine in 800 mL of THF

- 45 -

over a period of 5 min. and stir the mixture for 1 hr. at room temperature. Heat the mixture at reflux overnight, then cool to room temperature and dilute the mixture with 1 L of CH_2Cl_2 .

- 5 Wash with water (5 X 200 mL), and extract the aqueous wash with CHCl_3 (3 X 100 mL). Combine all of the organic solutions, wash with brine (3 X 200 mL) and dry over MgSO_4 . Concentrate *in vacuo* to a residue and chromatograph (silica gel, gradient of 5%, 7.5%, 10% $\text{MeOH}/\text{CH}_2\text{Cl}_2 + \text{NH}_4\text{OH}$) to give 18.49 g of the title compound as a racemic mixture.

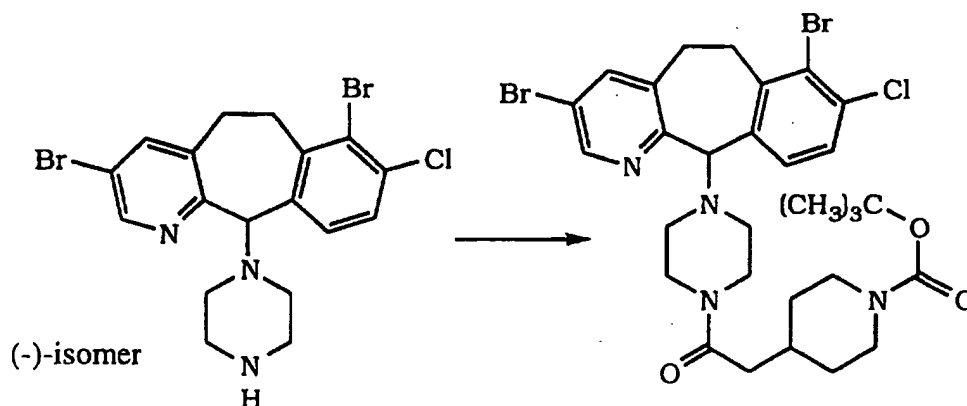
10 Step D - Separation of Enantiomers:



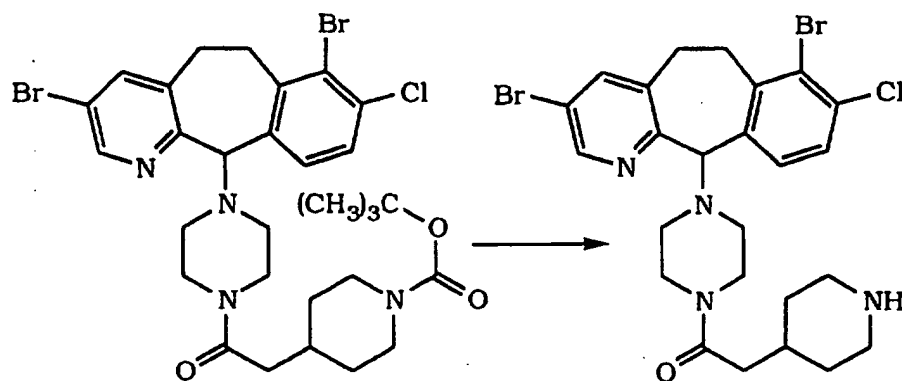
- The racemic title compound of Step C is separated by preparative chiral chromatography (Chiralpack AD, 5 cm X 50 cm column, flow rate 100 mL/min., 20% *i*PrOH/hexane + 0.2% diethylamine), to give 9.14 g of the (+)-isomer and 9.30 g of the (-)-isomer.

Physical chemical data for (+)-isomer: m.p. = 74.5°-77.5°C; Mass Spec. $\text{MH}^+ = 471.9$; $[\alpha]_{\text{D}}^{25} = +97.4^\circ$ (8.48 mg/ 2mL MeOH).

- Physical chemical data for (-)-isomer: m.p. = 82.9°-84.5°C; Mass Spec. $\text{MH}^+ = 471.8$; $[\alpha]_{\text{D}}^{25} = -97.4^\circ$ (8.32 mg/ 2mL MeOH).

Step E:

Combine 3.21 g (6.80 mmol) of the (-)-isomer product of Step D and 150 mL of anhydrous DMF. Add 2.15 g (8.8 mmol) of
 5 1-N-t-butoxycarbonylpiperidiny-4-acetic acid, 1.69 g (8.8 mmol) of DEC, 1.19 g (8.8 mmol) of HOBT and 0.97 mL (8.8 mmol) of N-methylmorpholine and stir the mixture at room temperature overnight. Concentrate *in vacuo* to remove the DMF and add 50 mL of saturated NaHCO₃ (aqueous). Extract with CH₂Cl₂ (2 X 250
 10 mL), wash the extracts with 50 mL of brine and dry over MgSO₄. Concentrate *in vacuo* to a residue and chromatograph (silica gel, 2% MeOH/CH₂Cl₂ + 10% NH₄OH) to give 4.75 g of the product. m.p. = 75.7°-78.5°C; Mass Spec.: MH⁺ = 697; [α]_D²⁵ = -5.5° (6.6 mg/2 mL MeOH).

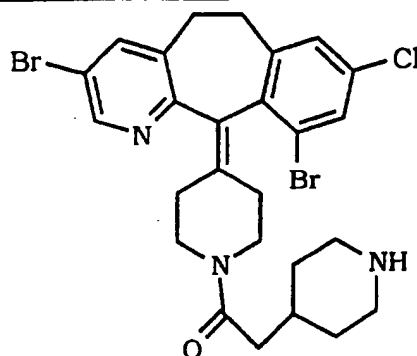
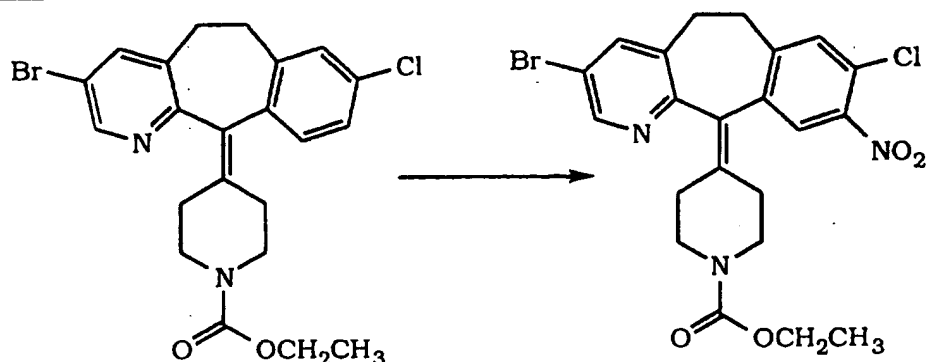
15 Step F:

Combine 4.70 g (6.74 mmol) of the product of Step E and 30 mL of MeOH, then add 50 mL of 10% H₂SO₄/dioxane in 10 mL aliquots over a 1 hr. period. Pour the mixture into 50 mL of
 20 water and add 15 mL of 50% NaOH (aqueous) to adjust to pH≈ 10-11. Filter to remove the resulting solids and extract the filtrate with CH₂Cl₂ (2 X 250 mL). Concentrate the aqueous layer *in vacuo* to remove the MeOH and extract again with 250 mL of

- 47 -

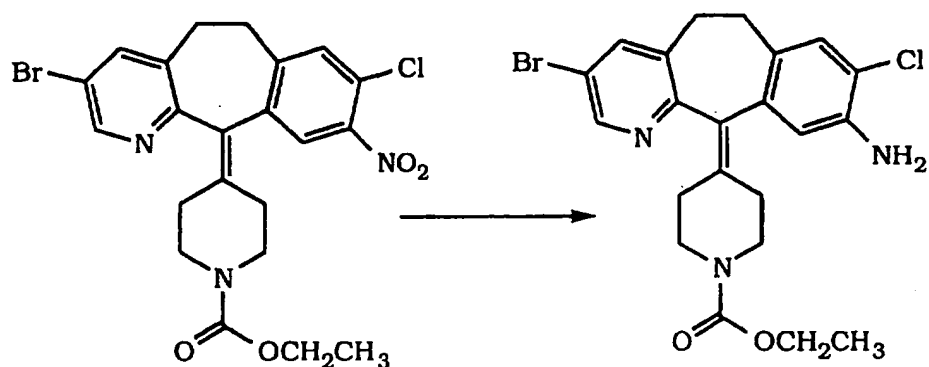
CH₂Cl₂. Dry the combined extracts over MgSO₄ and concentrate *in vacuo* to give the product. m.p. = 128.1°-131.5°C; Mass Spec.: MH⁺ = 597; $[\alpha]_D^{25} = -6.02^\circ$ (9.3 mg/2 mL MeOH).

5

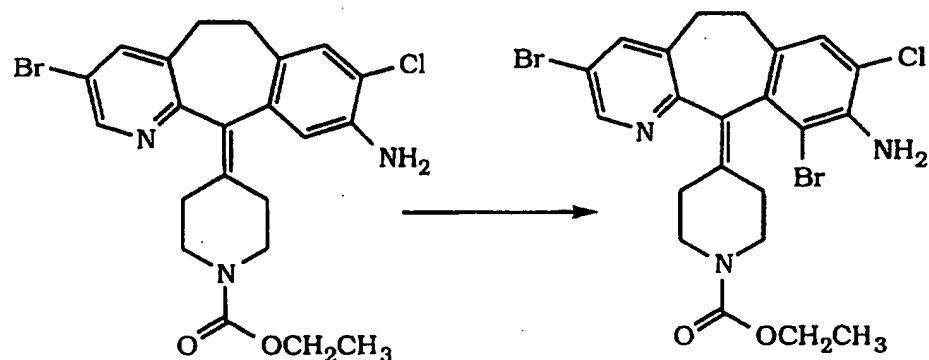
PREPARATIVE EXAMPLE 7Step A:

- Combine 15 g (38.5 mmol) of 4-(8-chloro-3-bromo-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)-1-piperidine-1-carboxylic acid ethyl ester and 150 mL of concentrated H₂SO₄ at -5°C, then add 3.89 g (38.5 mmol) of KNO₃ and stir for 4 hours. Pour the mixture into 3 L of ice and basify with 50% NaOH (aqueous). Extract with CH₂Cl₂, dry over MgSO₄, then filter and concentrate *in vacuo* to a residue. Recrystallize the residue from acetone to give 6.69 g of the product. ¹H NMR (CDCl₃, 200 MHz): 8.5 (s, 1H); 7.75 (s, 1H); 7.6 (s, 1H); 7.35 (s, 1H); 4.15 (q, 2H); 3.8 (m, 2H); 3.5-3.1 (m, 4H); 3.0-2.8 (m, 2H); 2.6-2.2 (m, 4H); 1.25 (t, 3H).

- 48 -

Step B:

Combine 6.69 g (13.1 mmol) of the product of Step A and 100 mL of 85% EtOH/water, then add 0.66 g (5.9 mmol) of CaCl_2 and 6.56 g (117.9 mmol) of Fe and heat the mixture at reflux overnight. Filter the hot reaction mixture through celite® and rinse the filter cake with hot EtOH. Concentrate the filtrate *in vacuo* to give 7.72 g of the product. Mass Spec.: $\text{MH}^+ = 478.0$

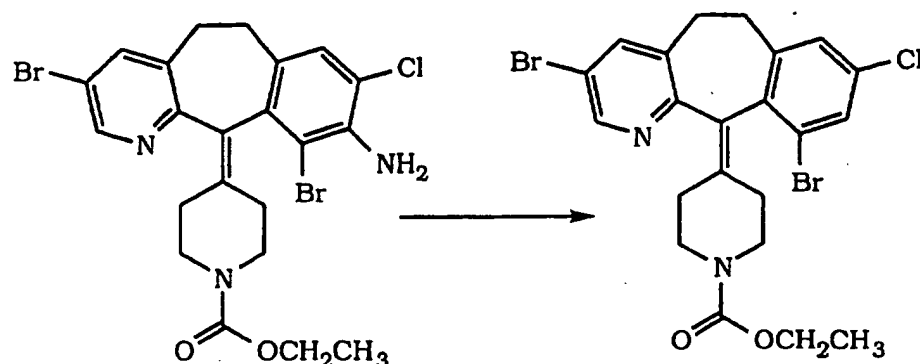
Step C:

10

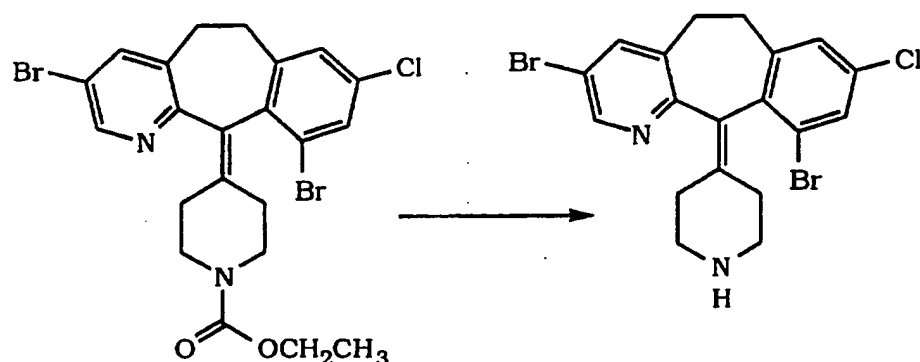
Combine 7.70 g of the product of Step B and 35 mL of HOAc, then add 45 mL of a solution of Br_2 in HOAc and stir the mixture at room temperature overnight. Add 300 mL of 1 N NaOH (aqueous), then 75 mL of 50% NaOH (aqueous) and extract with EtOAc. Dry the extract over MgSO_4 and concentrate *in vacuo* to a residue. Chromatograph the residue (silica gel, 20%-30% EtOAc/hexane) to give 3.47 g of the product (along with another 1.28 g of partially purified product). Mass Spec.: $\text{MH}^+ = 555.9$.

^1H NMR (CDCl_3 , 300 MHz): 8.5 (s, 1H); 7.5 (s, 1H); 7.15 (s, 1H); 4.5 (s, 2H); 4.15 (m, 3H); 3.8 (br s, 2H); 3.4-3.1 (m, 4H); 9-2.75 (m, 1H); 2.7-2.5 (m, 2H); 2.4-2.2 (m, 2H); 1.25 (m, 3H).

20

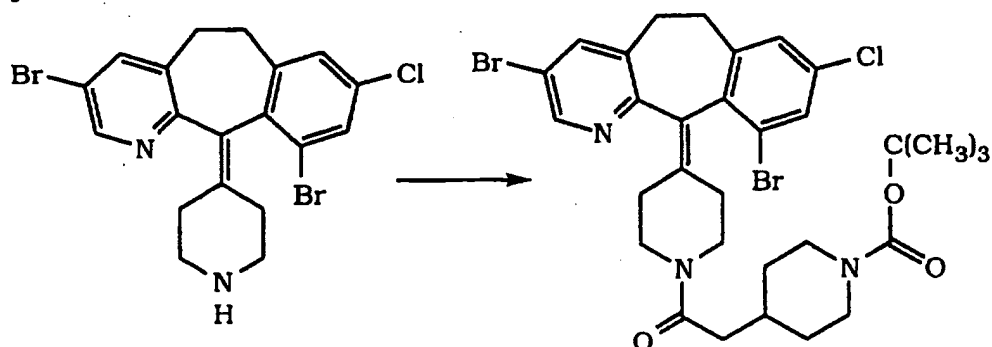
Step D:

- Combine 0.557 g (5.4 mmol) of t-butyl nitrite and 3 mL of DMF, and heat the mixture at to 60°-70°C. Slowly add (dropwise) a mixture of 2.00 g (3.6 mmol) of the product of Step C and 4 mL of DMF, then cool the mixture to room temperature. Add another 0.64 mL of t-butyl nitrite at 40°C and reheat the mixture to 60°-70°C for 0.5 hrs. Cool to room temperature and pour the mixture into 150 mL of water. Extract with CH₂Cl₂, dry the extract over MgSO₄ and concentrate *in vacuo* to a residue. Chromatograph the residue (silica gel, 10%-20% EtOAc/hexane) to give 0.74 g of the product. Mass Spec.: MH⁺ = 541.0.
- ¹H NMR (CDCl₃, 200 MHz): 8.52 (s, 1H); 7.5 (d, 2H); 7.2 (s, 1H); 4.15 (q, 2H); 3.9-3.7 (m, 2H); 3.5-3.1 (m, 4H); 3.0-2.5 (m, 2H); 2.4-2.2 (m, 2H); 2.1-1.9 (m, 2H); 1.26 (t, 3H).

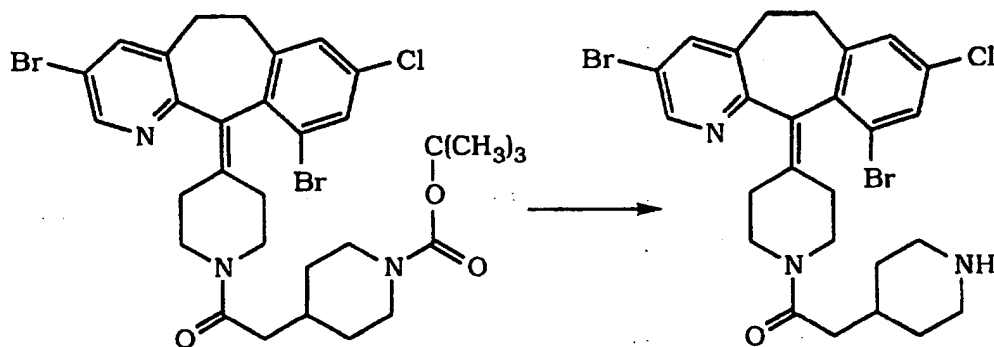
Step E:

- Combine 0.70 g (1.4 mmol) of the product of Step D and 8 mL of concentrated HCl (aqueous) and heat the mixture at reflux overnight. Add 30 mL of 1 N NaOH (aqueous), then 5 mL of 50% NaOH (aqueous) and extract with CH₂Cl₂. Dry the extract over MgSO₄ and concentrate *in vacuo* to give 0.59 g of the title compound. Mass Spec.: M⁺ = 468.7. m.p. = 123.9°-124.2°C.

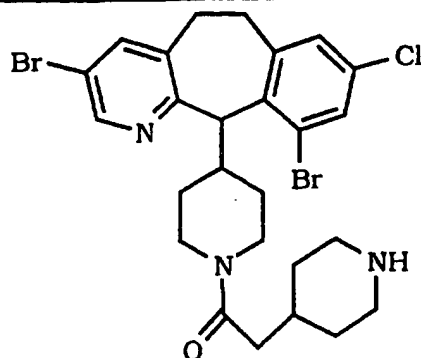
- 50 -

Step F:

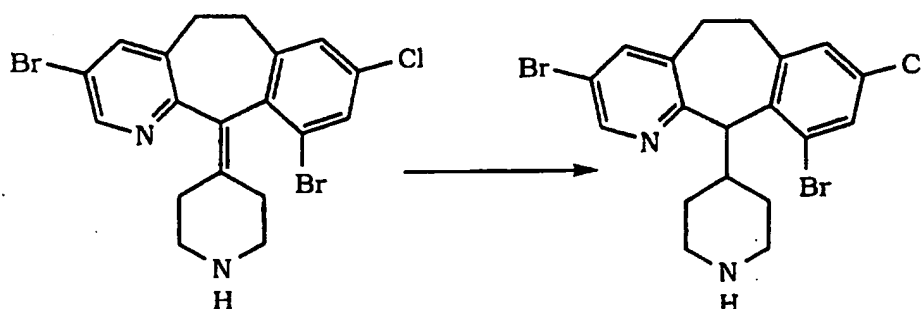
React 6.0 g (12.8 mmol) of the title compound from Step E and with 3.78 g (16.6 mmol) of 1-N-t-butoxycarbonylpiperidinyl-4-acetic acid using substantially the same procedures as described for Preparative Example 5, Step C, to give 8.52 g of the product. Mass Spec.: $MH^+ = 694.0$ (FAB). 1H NMR ($CDCl_3$, 200 MHz): 8.5 (d, 1H); 7.5 (d, 2H); 7.2 (d, 1H); 4.15-3.9 (m, 3H); 3.8-3.6 (m, 1H); 3.5-3.15 (m, 3H); 2.9 (d, 2H); 2.8-2.5 (m, 4H); 2.4-1.8 (m, 6H); 1.8-1.6 (br d, 2H); 1.4 (s, 9H); 1.25-1.0 (m, 2H).

Step G:

Combine 8.50 g of the product of Step F and 60 mL of CH_2Cl_2 , then cool to $0^\circ C$ and add 55 mL of TFA. Stir the mixture for 3 h at $0^\circ C$, then add 500 mL of 1 N NaOH (aqueous) followed by 30 mL of 50% NaOH (aqueous). Extract with CH_2Cl_2 , dry over $MgSO_4$ and concentrate *in vacuo* to give 7.86 g of the product. Mass Spec.: $M^+ = 593.9$ (FAB). 1H NMR ($CDCl_3$, 200 MHz): 8.51 (d, 1H); 7.52 (d of d, 2H); 7.20 (d, 1H); 4.1-3.95 (m, 2H); 3.8-3.65 (m, 2H); 3.5-3.05 (m, 5H); 3.0-2.5 (m, 6H); 2.45-1.6 (m, 6H); 1.4-1.1 (m, 2H).

PREPARATIVE EXAMPLE 8

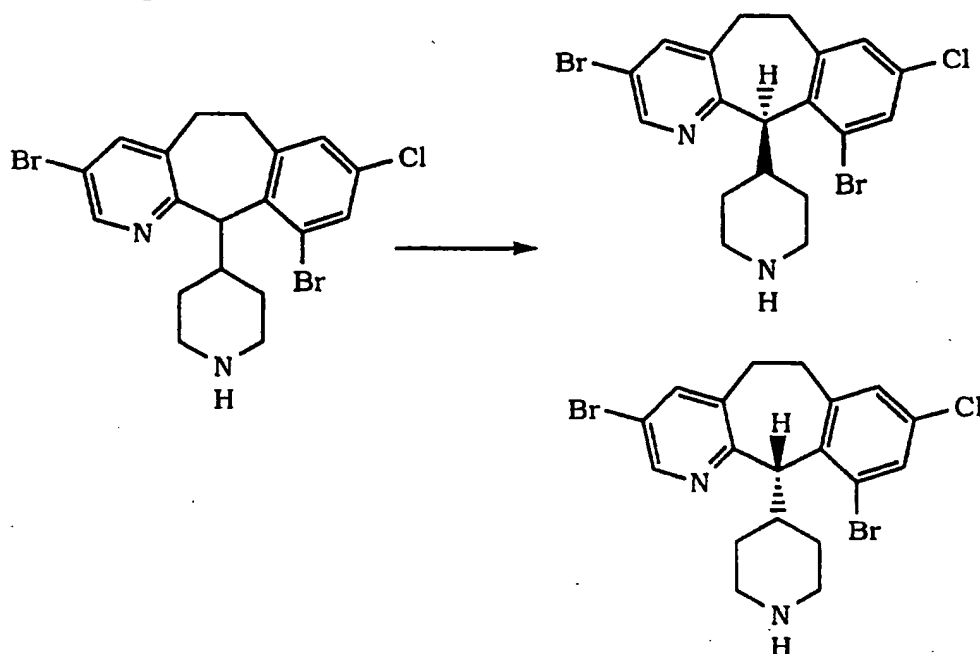
[racemic as well as (+)- and (-)-isomers]

Step A:

5

- Prepare a solution of 8.1 g of the title compound from Preparative Example 7, Step E, in toluene and add 17.3 mL of a 1M solution of DIBAL in toluene. Heat the mixture at reflux and slowly add (dropwise) another 21 mL of 1 M DIBAL/toluene solution over a period of 40 min. Cool the reaction mixture to about 0°C and add 700 mL of 1 M HCl (aqueous). Separate and discard the organic phase. Wash the aqueous phase with CH₂Cl₂, discard the extract, then basify the aqueous phase by adding 50% NaOH (aqueous). Extract with CH₂Cl₂, dry the extract over MgSO₄ and concentrate *in vacuo* to give 7.30 g of the title compound, which is a racemic mixture of enantiomers.
- 10
- 15

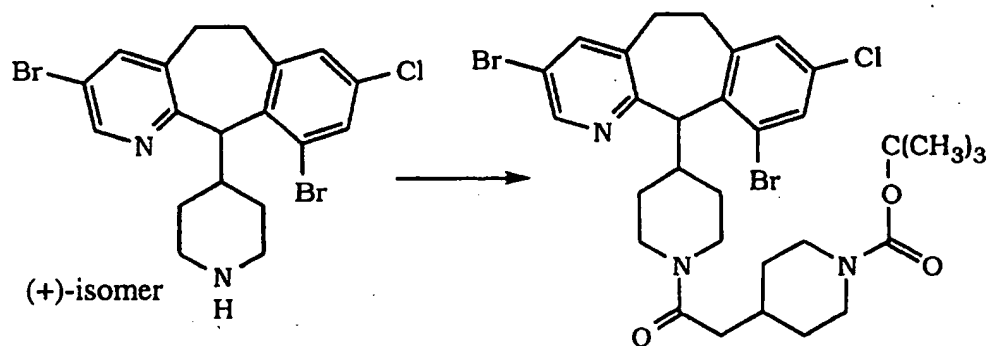
- 52 -

Step B - Separation of Enantiomers:

The racemic title compound of Step A is separated by preparative chiral chromatography (Chiralpack AD, 5 cm X 50 cm column, using 20% iPrOH/hexane + 0.2% diethylamine), to give the (+)-isomer and the (-)-isomer of the title compound.

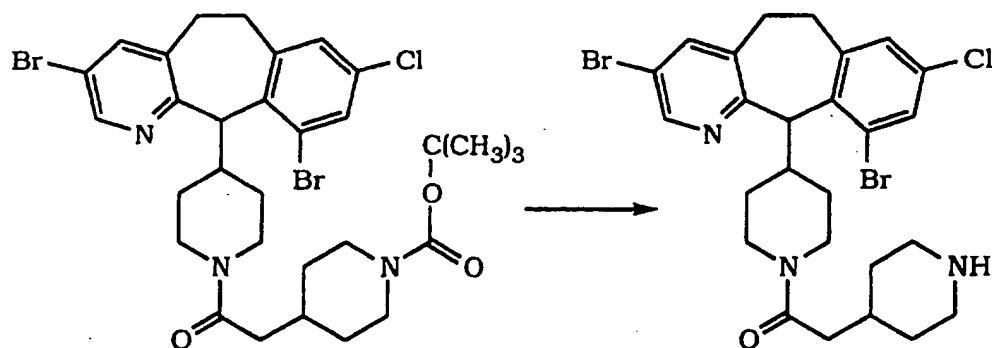
Physical chemical data for (+)-isomer: m.p. = 148.8°C;
Mass Spec. $MH^+ = 469$; $[\alpha]_D^{25} = +65.6^\circ$ (12.93 mg/ 2mL MeOH).

Physical chemical data for (-)-isomer: m.p. = 112°C;
10 Mass Spec. $MH^+ = 469$; $[\alpha]_D^{25} = -65.2^\circ$ (3.65 mg/ 2mL MeOH).

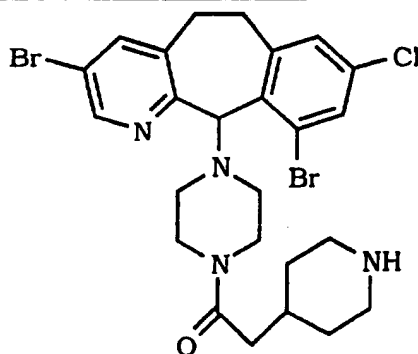
Step C:

React 1.33 g of the (+)-isomer of the title compound of Preparative Example 8, Step B, with 1.37 g of 1-N-t-butoxycarbonylpiperidinyl-4-acetic acid using substantially the same procedures as described for Preparative Example 5, Step C, to
15 give 2.78 g of the product. Mass Spec.: $MH^+ = 694.0$ (FAB); $[\alpha]_D^{25} = +34.1^\circ$ (5.45 mg/2 mL, MeOH).

- 53 -

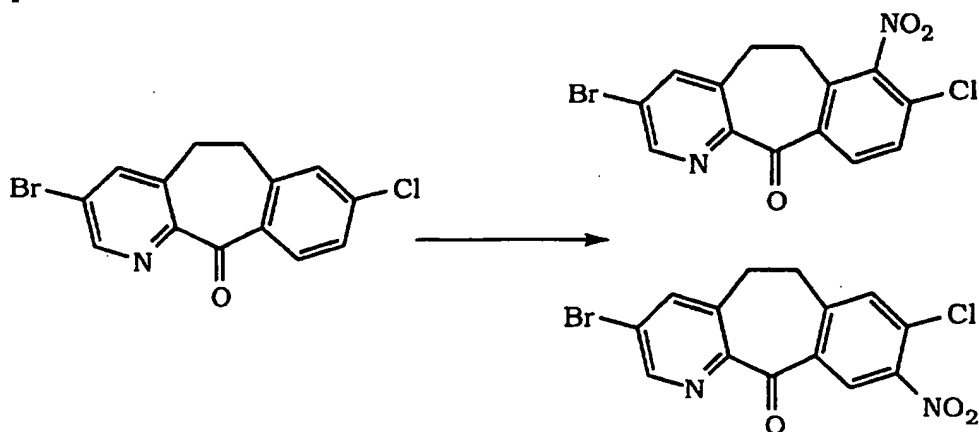
Step D:

Treat 2.78 g of the product of Step C via substantially the same procedure as described for Preparative Example 5, Step D, to give 1.72 g of the product. m.p. = 104.1°C; Mass Spec.: MH^+ = 594; $[\alpha]_D^{25} = +53.4^\circ$ (11.42 mg/2 mL, MeOH).

PREPARATIVE EXAMPLE 9

10

[racemic as well as (+)- and (-)-isomers]

Step A:

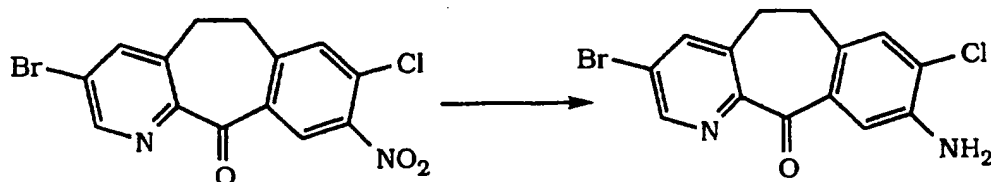
Combine 40.0 g (0.124 mole) of the starting ketone and 200 mL of H_2SO_4 and cool to 0°C. Slowly add 13.78 g (0.136 mole) of KNO_3 over a period of 1.5 hrs., then warm to room temperature and stir overnight. Work up the reaction using

15

- 54 -

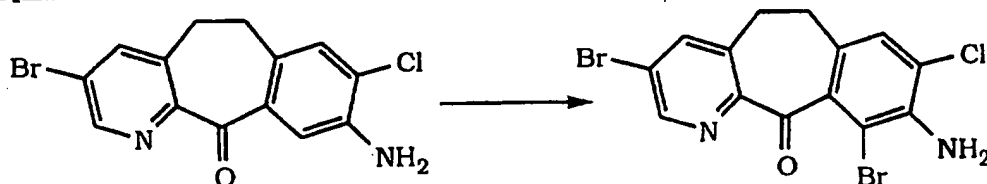
substantially the same procedure as described for Preparative Example 4, Step A. Chromatograph (silica gel, 20%, 30%, 40%, 50% EtOAc/hexane, then 100% EtOAc) to give 28 g of the 9-nitro product, along with a smaller quantity of the 7-nitro product and 19 g of a mixture of the 7-nitro and 9-nitro compounds.

Step B:



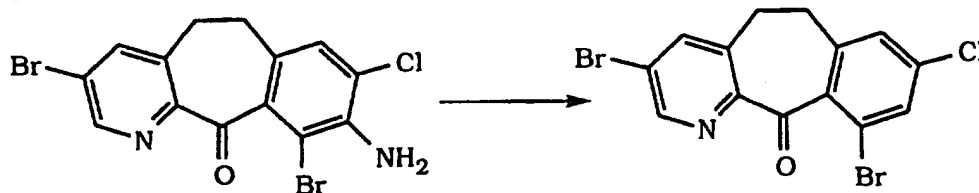
React 28 g (76.2 mmol) of the 9-nitro product of Step A, 400 mL of 85% EtOH/water, 3.8 g (34.3 mmol) of CaCl₂ and 38.28 g (0.685 mole) of Fe using substantially the same procedure as described for Preparative Example 4, Step C, to give 24 g of the product

Step C:



Combine 13 g (38.5 mmol) of the product of Step B, 140 mL of HOAc and slowly add a solution of 2.95 mL (57.8 mmol) of Br₂ in 10 mL of HOAc over a period of 20 min. Stir the reaction mixture at room temperature, then concentrate *in vacuo* to a residue. Add CH₂Cl₂ and water, then adjust to pH = 8-9 with 50% NaOH (aqueous). Wash the organic phase with water, then brine and dry over Na₂SO₄. Concentrate *in vacuo* to give 11.3 g of the product.

Step D:



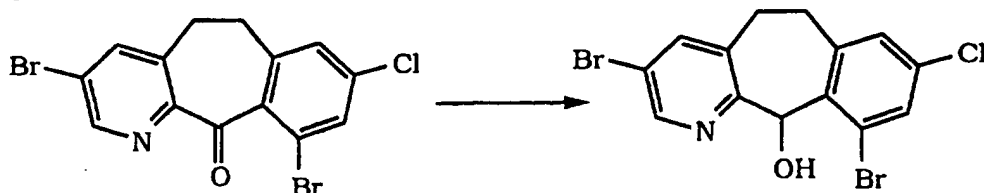
25

Cool 100 mL of concentrated HCl (aqueous) to 0°C, then add 5.61 g (81.4 mmol) of NaNO₂ and stir for 10 min. Slowly add (in portions) 11.3 g (27.1 mmol) of the product of Step C and stir

- 55 -

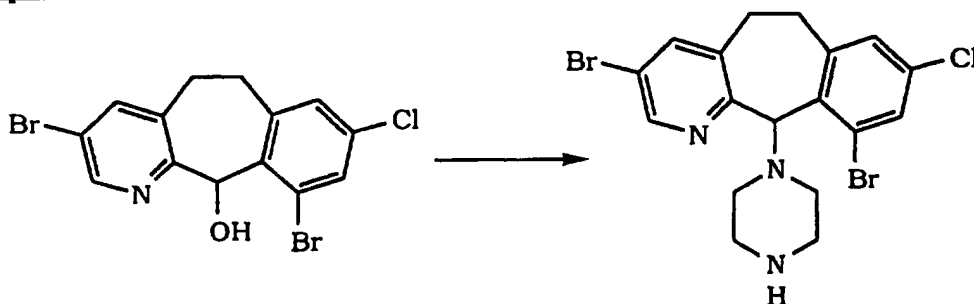
- the mixture at 0°-3°C for 2.25 hrs. Slowly add (dropwise) 180 mL of 50% H₃PO₂ (aqueous) and allow the mixture to stand at 0°C overnight. Slowly add (dropwise) 150 mL of 50% NaOH over 30 min., to adjust to pH = 9, then extract with CH₂Cl₂. Wash the
- 5 extract with water, then brine and dry over Na₂SO₄. Concentrate *in vacuo* to a residue and chromatograph (silica gel, 2% EtOAc/CH₂Cl₂) to give 8.6 g of the product.

Step E:



- 10 Combine 8.6 g (21.4 mmol) of the product of Step D and 300 mL of MeOH and cool to 0°-2°C. Add 1.21 g (32.1 mmol) of NaBH₄ and stir the mixture at ~0°C for 1 hr. Add another 0.121 g (3.21 mmol) of NaBH₄, stir for 2 hr. at 0°C, then let stand overnight at 0°C. Concentrate *in vacuo* to a residue then partition
- 15 the residue between CH₂Cl₂ and water. Separate the organic phase and concentrate *in vacuo* (50°C) to give 8.2 g of the product.

Step F:



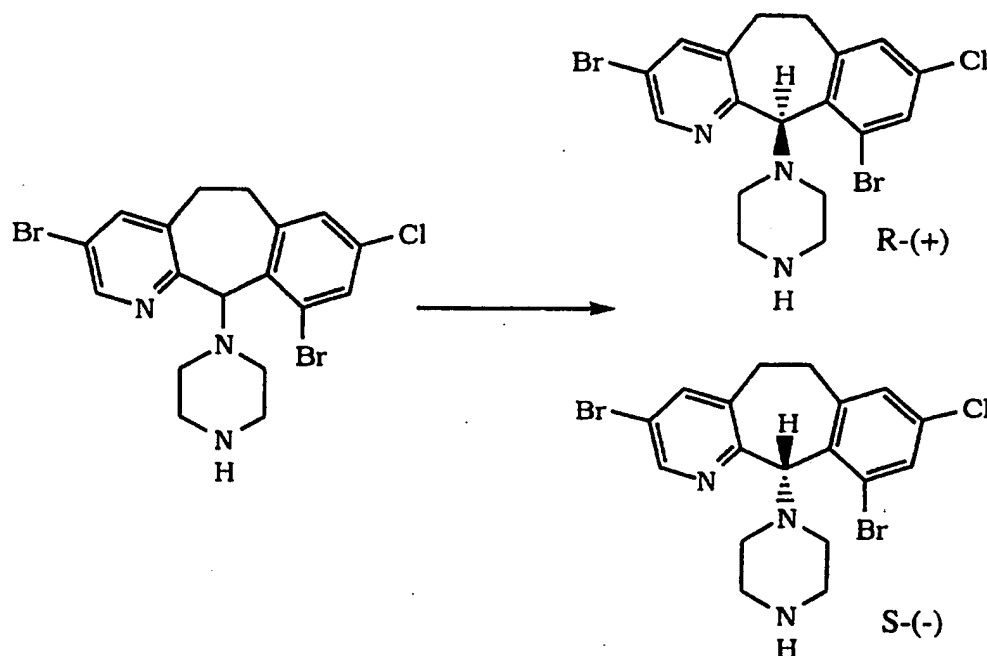
- 20 Combine 8.2 g (20.3 mmol) of the product of Step E and 160 mL of CH₂Cl₂, cool to 0°C, then slowly add (dropwise) 14.8 mL (203 mmol) of SOCl₂ over a 30 min. period. Warm the mixture to room temperature and stir for 4.5 hrs., then concentrate *in vacuo* to a residue, add CH₂Cl₂ and wash with 1 N
- 25 NaOH (aqueous) then brine and dry over Na₂SO₄. Concentrate *in vacuo* to a residue, then add dry THF and 8.7 g (101 mmol) of piperazine and stir at room temperature overnight. Concentrate *in vacuo* to a residue, add CH₂Cl₂, and wash with 0.25 N NaOH (aqueous), water, then brine. Dry over Na₂SO₄ and concentrate *in*

- 56 -

vacuo to give 9.46 g of the crude product. Chromatograph (silica gel, 5% MeOH/CH₂Cl₂ + NH₃) to give 3.59 g of the title compound, as a racemate. ¹H NMR (CDCl₃, 200 MHz): 8.43 (d, 1H); 7.55 (d, 1H); 7.45 (d, 1H); 7.11 (d, 1H); 5.31 (s, 1H);

- 5 4.86-4.65 (m, 1H); 3.57-3.40 (m, 1H); 2.98-2.55 (m, 6H); 2.45-2.20 (m, 5H).

Step G - Separation of Enantiomers:



- The racemic title compound from Step F (5.7 g) is
 10 chromatographed as described for Preparative Example 6, Step D, using 30% iPrOH/hexane + 0.2% diethylamine, to give 2.88 g of the R-(+)-isomer and 2.77 g of the S-(-)-isomer of the title compound.

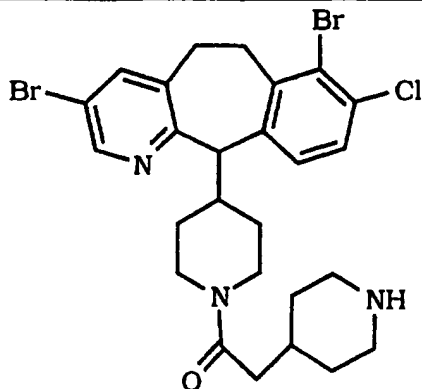
- Physical chemical data for the R-(+)-isomer: Mass Spec.
 15 MH⁺ = 470.0; [α]_D²⁵ = +12.1° (10.9 mg/ 2mL MeOH).

Physical chemical data for the S-(-)-isomer: Mass Spec.
 MH⁺ = 470.0; [α]_D²⁵ = -13.2° (11.51 mg/ 2mL MeOH).

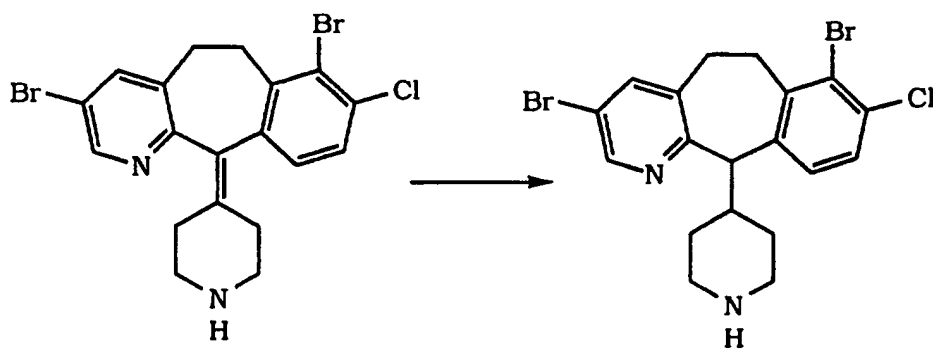
Step H:

- Following essentially the same procedure as Preparative
 20 Example 5, Steps C and D, the racemic title compound of Preparative Example 9 is obtained from the racemic compound of Step F. Similarly, using the (-)- or (+)- isomer from Step G, the (-)- or (+)-isomer of the title compound of Preparative Example 9 is obtained, respectively.

- 57 -

PREPARATIVE EXAMPLE 10

[racemic as well as (+)- and (-)-isomers]

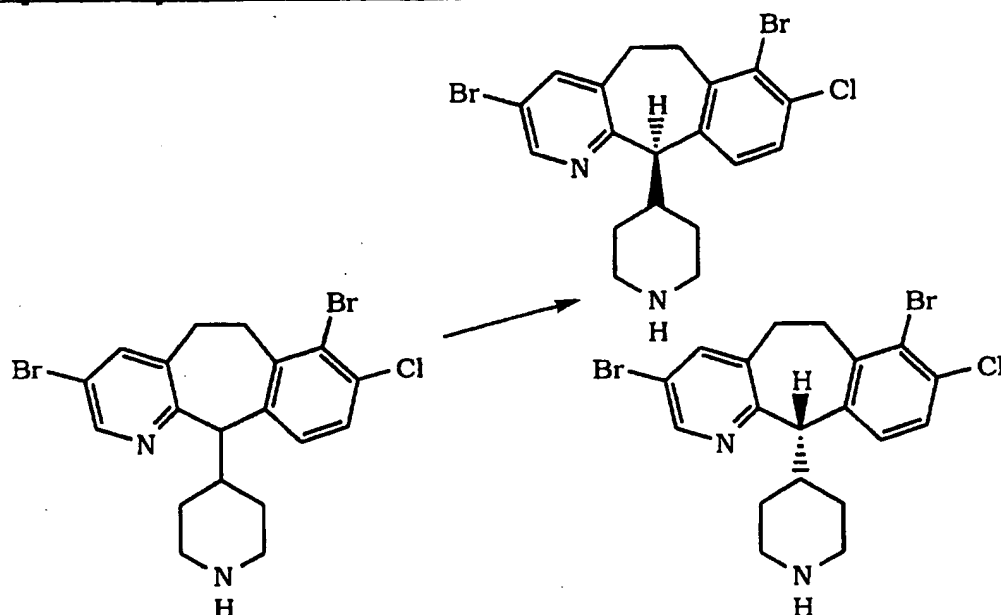
Step A:

5

Combine 13 g (33.3 mmol) of the title compound from Preparative Example 4, Step E, and 300 mL of toluene at 20°C, then add 32.5 mL (32.5 mmol) of a 1 M solution of DIBAL in toluene. Heat the mixture at reflux for 1 hr., cool to 20°C, add another 32.5 mL of 1 M DIBAL solution and heat at reflux for 1 hr. Cool the mixture to 20°C and pour it into a mixture of 400 g of ice, 500 mL of EtOAc and 300 mL of 10% NaOH (aqueous). Extract the aqueous layer with CH₂Cl₂ (3 x 200 mL), dry the organic layers over MgSO₄, then concentrate *in vacuo* to a residue. Chromatograph (silica gel, 12% MeOH/CH₂Cl₂ + 4% NH₄OH) to give 10.4 g of the title compound as a racemate. Mass Spec.: MH⁺ = 469(FAB). partial ¹H NMR (CDCl₃, 400 MHz): 8.38 (s, 1H); 7.57 (s, 1H); 7.27 (d, 1H); 7.06 (d, 1H); 3.95 (d, 1H).

15

- 58 -

Step B - Separation of Enantiomers:

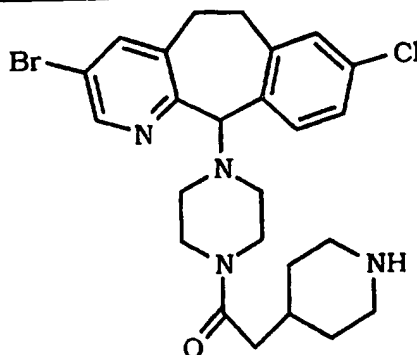
The racemic title compound of Step A is separated by preparative chiral chromatography (Chiralpack AD, 5 cm X 50 cm column, using 5% iPrOH/hexane + 0.2% diethylamine), to give the (+)-isomer and the (-)-isomer of the title compound.

Physical chemical data for (+)-isomer: Mass Spec. $MH^+ = 469$ (FAB); $[\alpha]_D^{25} = +43.5^\circ$ ($c=0.402$, EtOH); partial 1H NMR ($CDCl_3$, 400 MHz): 8.38 (s, 1H); 7.57 (s, 1H); 7.27 (d, 1H); 7.05 (d, 1H); 3.95 (d, 1H).

Physical chemical data for (-)-isomer: Mass Spec. $MH^+ = 469$ (FAB); $[\alpha]_D^{25} = -41.8^\circ$ ($c=0.328$ EtOH); partial 1H NMR ($CDCl_3$, 400 MHz): 8.38 (s, 1H); 7.57 (s, 1H); 7.27 (d, 1H); 7.05 (d, 1H); 3.95 (d, 1H).

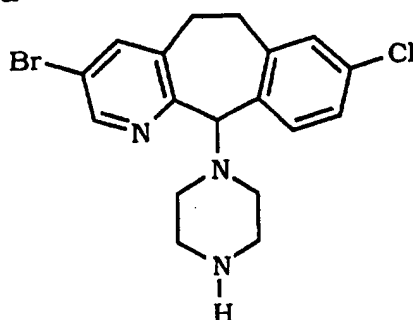
15 Step C:

Following the procedure of Preparative Example 9, Step H, the racemic compound, the (+)-isomer or the (-)-isomer of the title compound of Preparative Example 10 can be obtained.

PREPARATIVE EXAMPLE 11

[racemic as well as R-(+)- and S-(-)-isomers]

The compound



5

is prepared according to the procedures of Preparative Example 40 of WO 95/10516 (published April 20, 1995), by following the procedures described in Example 193 of WO 95/10516.

10 The (+)- and (-)-isomers can be separated by following essentially the same procedure as Step D of Preparative Example 6.

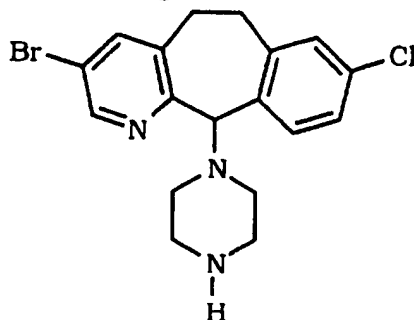
Physical chemical data for the R-(+)-isomer: ^{13}C NMR (CDCl_3): 155.8 (C); 146.4 (CH); 140.5 (CH); 140.2 (C); 136.2 (C); 135.3 (C); 133.4 (C); 132.0 (CH); 129.9 (CH); 125.6 (CH); 15 119.3 (C); 79.1 (CH); 52.3 (CH_2); 52.3 (CH); 45.6 (CH_2); 45.6 (CH_2); 30.0 (CH_2); 29.8 (CH_2). $[\alpha]_{\text{D}}^{25} = +25.8^\circ$ (8.46 mg/2 mL MeOH).

Physical chemical data for the S-(-)-isomer: ^{13}C NMR (CDCl_3): 155.9 (C); 146.4 (CH); 140.5 (CH); 140.2 (C); 136.2 20 (C); 135.3 (C); 133.3 (C); 132.0 (CH); 129.9 (CH); 125.5 (CH); 119.2 (C); 79.1 (CH); 52.5 (CH_2); 52.5 (CH); 45.7 (CH_2); 45.7 (CH_2); 30.0 (CH_2); 29.8 (CH_2). $[\alpha]_{\text{D}}^{25} = -27.9^\circ$ (8.90 mg/2 mL MeOH).

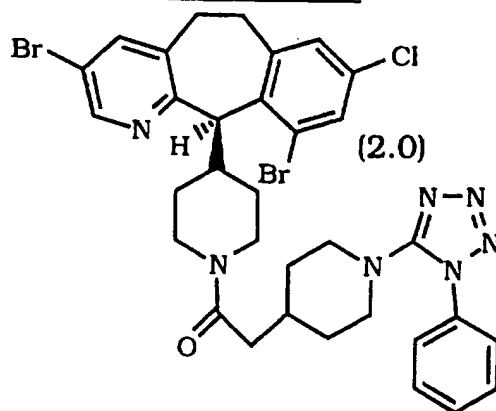
25 Following essentially the same procedure as Preparative Example 5, Steps C and D, the racemic compound, (+)-isomer or

- 60 -

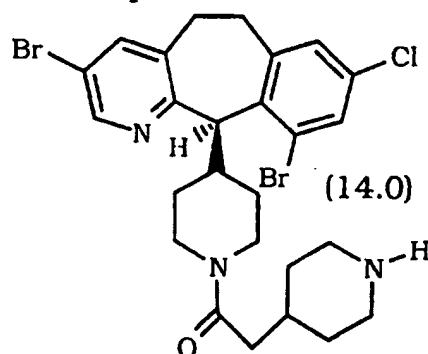
(-)-isomer of the title compound of Preparative Example 11 can be obtained from the corresponding racemic compound, (+)-isomer or (-)-isomer of the compound



5

EXAMPLE 1

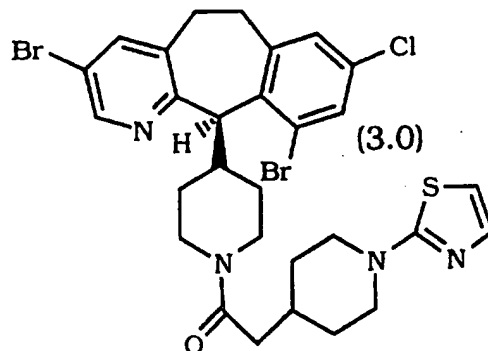
A mixture of the compound of Formula 14.0



- 10 (Preparative Example 8) (0.10 g, 0.17 mmol), anhydrous dimethylformamide (5 mL), 5-chloro-1-phenyl-1H-tetrazole (0.03 g, 0.19 mmol) and anhydrous sodium carbonate (0.04 g, 0.34 mmol) were stirred at room temperature overnight. The mixture was concentrated *in vacuo*, diluted with dichloromethane,
- 15 washed with water and dried over anhydrous magnesium sulfate. Filtration and concentration *in vacuo* afforded a yellow oil (0.10 g). Purification by flash column chromatography (silica gel) using 50% ethyl acetate-hexane, followed by 100% ethyl acetate

provided the compound of Formula 2.0 (0.06 g, 46%, mp 133°C (dec)).

EXAMPLE 2



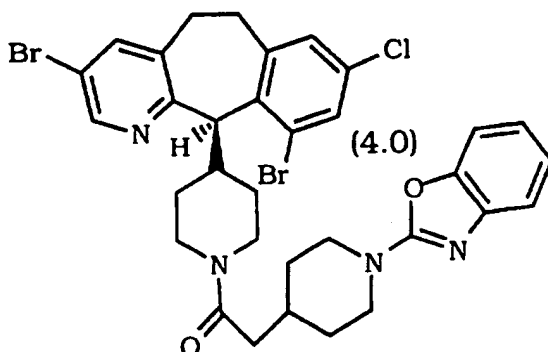
5

To the compound of Formula 14.0 (Preparative Example 8) (0.15g, 0.25 mmol), anhydrous dimethylformamide (5 mL), 2-bromothiazole (0.08 g, 0.50 mmol) and anhydrous sodium carbonate (0.05 g, 0.50 mmol) were stirred at room temperature overnight, then heated at reflux for 2.5 h. The mixture was concentrated *in vacuo*, diluted with dichloromethane and washed with 1 M hydrochloric acid, then with 1 N aqueous sodium hydroxide and dried over anhydrous magnesium sulfate. Filtration and concentration *in vacuo* afforded a sticky foam (0.13 g). Purification by preparative plate chromatography (silica gel) using 2% methanol-dichloromethane provided the compound of Formula 3.0 (0.07 g, 41%, mp 117.6°C (dec)).

10

15

EXAMPLE 3



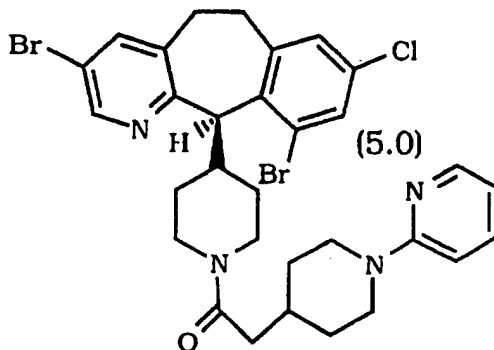
20

To the compound of Formula 14.0 (Preparative Example 8) (0.15g, 0.25 mmol), anhydrous dimethylformamide (5 mL), 2-chlorobenzoxazole (0.08 g, 0.50 mmol) and anhydrous sodium carbonate (0.05 g, 0.50 mmol) were stirred at room temperature overnight. The mixture was concentrated *in vacuo*, diluted with

25

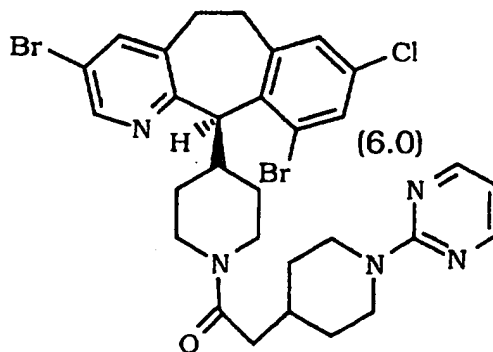
dichloromethane and washed with 1 M hydrochloric acid, then with 1 N aqueous sodium hydroxide and dried over anhydrous magnesium sulfate. Filtration and concentration *in vacuo* afforded a foam (0.17 g). Purification by preparative plate chromatography (silica gel) using 2% methanol-dichloromethane provided the compound of Formula 4.0 (0.08 g, 44%, mp 125.6°C).

EXAMPLE 4



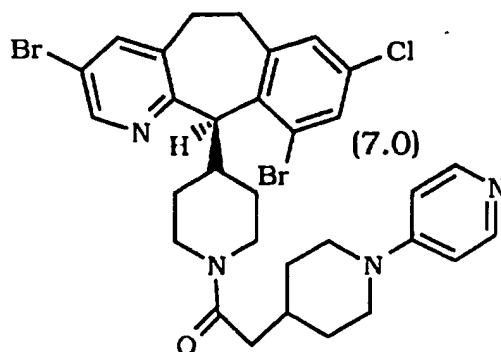
To the compound of Formula 14.0 (Preparative Example 8) (0.15 g, 0.25 mmol), anhydrous dimethylformamide (5 mL), 2-bromopyridine (0.16 g, 1.0 mmol) and anhydrous sodium carbonate (0.05 g, 0.50 mmol) were stirred at room temperature overnight, then at reflux for 1 h. The mixture was concentrated *in vacuo*, diluted with dichloromethane and washed with 1 M hydrochloric acid, then with 1 N aqueous sodium hydroxide and dried over anhydrous magnesium sulfate. Filtration and concentration *in vacuo* afforded a yellow oil (0.24 g). Purification by preparative plate chromatography (silica gel) using 2% methanol-dichloromethane provided the compound of Formula 5.0 (0.08 g, 47%, mp 91.3°C).

EXAMPLE 5



- 63 -

To the compound of Formula 14.0 (Preparative Example 8) (0.15 g, 0.25 mmol), anhydrous dimethylformamide (5 mL), 2-bromopyrimidine (0.16 g, 1.0 mmol) and anhydrous sodium carbonate (0.05 g, 0.50 mmol) were stirred at room temperature for 48 h. The mixture was concentrated *in vacuo*, diluted with dichloromethane and washed with 1 M hydrochloric acid, then with 1 N aqueous sodium hydroxide and dried over anhydrous magnesium sulfate. Filtration and concentration *in vacuo* afforded a yellow oil (0.36 g). Purification by preparative plate chromatography (silica gel) using 5% methanol-dichloromethane provided the compound of Formula 6.0 (0.09 g, 53%, mp 103.3°C).

EXAMPLE 6

15

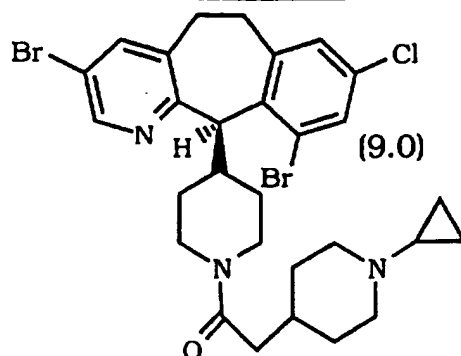
If one were to follow this procedure then one would obtain the compound of Formula 7.0.

To the compound of Formula 14.0 (Preparative Example 8) (0.15 g, 0.25 mmol), anhydrous dioxane (2 mL), 4-chloropyridine hydrochloride (0.04 g, 0.27 mmol) and anhydrous sodium carbonate (0.07 g, 0.62 mmol) are stirred at 115°C for 3 days. The mixture is cooled to room temperature, concentrated *in vacuo*, diluted with dichloromethane and water, and washed with 1M HCl (aq). The organic phase is washed with 1M NaOH (aq), dried over MgSO₄, filtered and concentrated by rotovap, pump. This provides the compound of Formula 7.0.

20

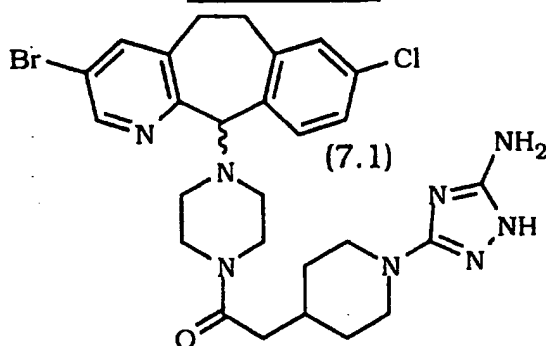
25

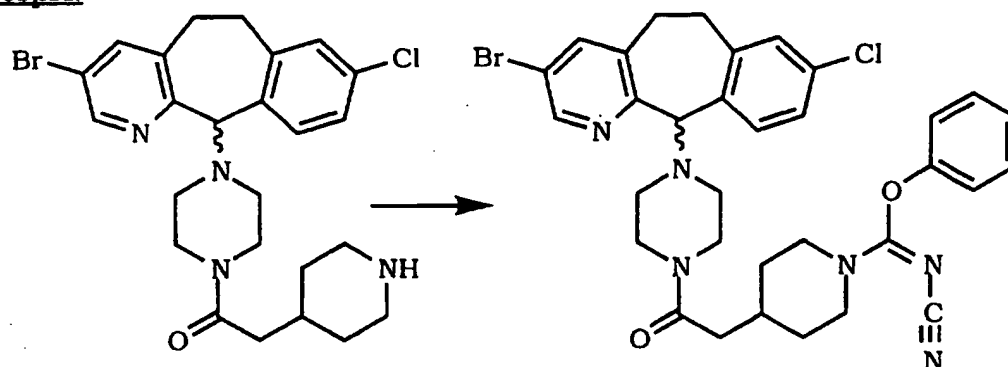
- 64 -

EXAMPLE 7

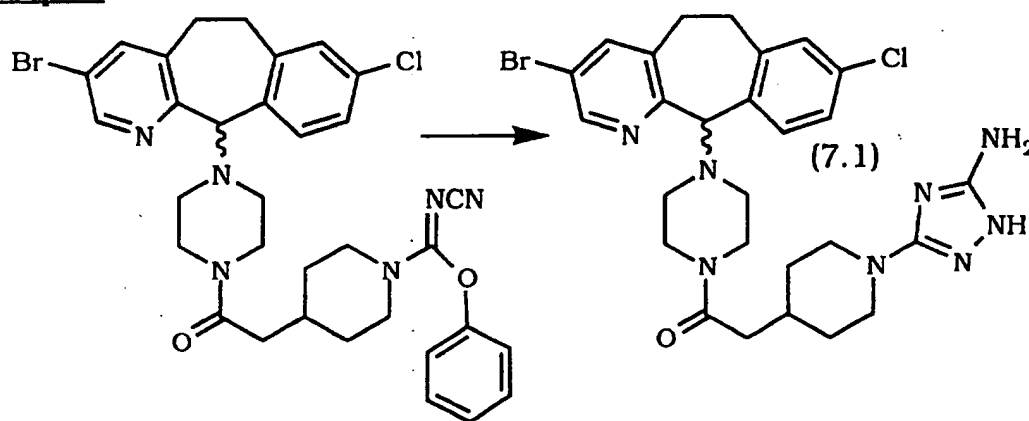
If this procedure is followed the compound of Formula 9.0 would be obtained.

- 5 To the compound of Formula 14.0 (Preparative Example 8), anhydrous dimethylformamide, bromocyclopropane and anhydrous sodium hydride are stirred together. The mixture is cooled to room temperature, diluted with water, filtered and the solids are washed with water. The solids are diluted with
- 10 dichloromethane, are washed with 1 M hydrochloric acid, then with 1 N aqueous sodium hydroxide and are dried over anhydrous magnesium sulfate. Filtration, concentration *in vacuo* and purification by preparative plate chromatography (silica gel) using 5% methanol-dichloromethane and concentrated ammonium
- 15 hydroxide provides the compound of Formula 9.0.

EXAMPLE 8

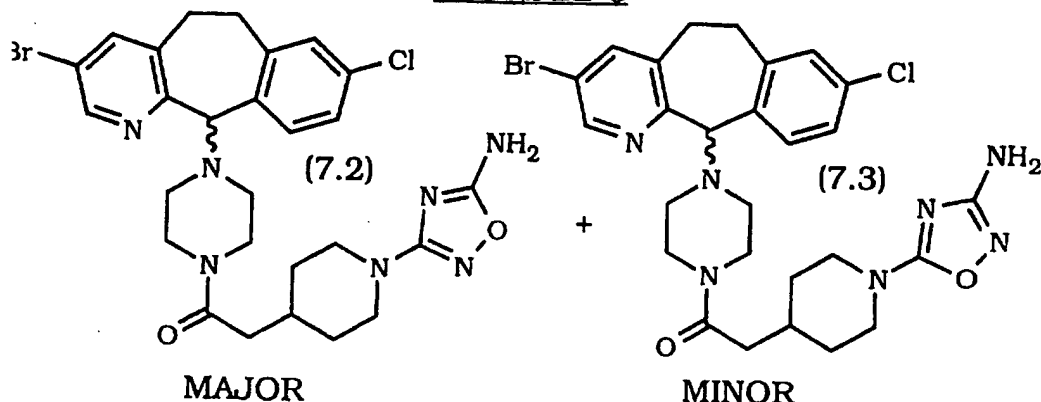
Step A:

- 5 1-(3-Bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]-
cyclohepta[1,2-b] pyridin-11-yl)-4-[(4-piperidiny)acetyl]-
piperazine (Preparative Example 11) (2.5g) (1 equivalent) and
diphenylcyanocarbonimidate (1.38g) (1.2 equivalents) were
dissolved in 2-propanol (65ml) and the solution was heated at
80°C under reflux and under nitrogen for 24h. The mixture was
evaporated to dryness and the product was chromatographed on a
10 silica gel column (60X2.5cm) using neat ethyl acetate as the
eluant to give the title compound (2.7921g; 87%), FABMS: m/z
661 (MH⁺).

Step B:

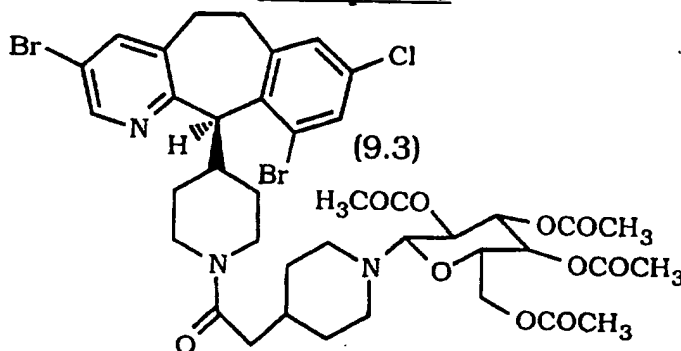
- 15 Phenyl 4-[2-[4-(3-bromo-8-chloro-6,11-dihydro-5H-
benzo[5,6] cyclohepta[1,2-b]pyridin-11-yl)-1-piperaziny]-2-
oxoethyl]-N-cyano-1-piperidinecarboximidate (Step A) (1
equivalent) is dissolved in methanol. Hydrazine hydrate (1
equivalent) is added and the mixture is stirred at 25°C for 1h.
20 The mixture is evaporated to dryness and chromatographed on
silica gel to give the title compound of Formula 7.1 ([5-[4-[2-[4-
(3-bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-

b)pyridin-11-yl)-1-piperazinyl]-2-oxoethyl]-1-piperidinyl]-3-amino-1,2,4-triazole).

EXAMPLE 9

- 5 Phenyl 4-[2-[4-(3-bromo-8-chloro-6,11-dihydro-5H-benzo[5,6] cyclohepta[1,2-b]pyridin-11-yl)-1-piperazinyl]-2-oxoethyl]-N-cyano-1-piperidine-carboximidate (Step A of Example 8) (1 equivalent) is dissolved in methanol.
- 10 Hydroxylamine (1 equivalent) is added and the mixture is stirred at 25°C for 1h. The mixture is evaporated to dryness and chromatographed on silica gel to give the title compounds of Formulas 7.2 ((3-[4-[2-[4-(3-bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-1-piperazinyl]-2-oxoethyl]-1-piperidinyl]-5-amino-1,2,4-oxadiazole) and 7.3 ((5-[4-[2-[4-(3-bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-1-piperazinyl]-2-oxoethyl]-1-piperidinyl]-3-amino-1,2,4-oxadiazole).
- 15

20

Example 10

To the compound of Formula 14.0 (Preparative Example 8) (0.20 g, 0.34 mmol) dissolved in 1,4-dioxane (5 mL) was added anhydrous sodium carbonate (0.07 g, 0.68 mmol) and tetra-

- 67 -

acetoxymethyl- α -D-glucose (0.15 g, 1.1 eq). After stirring at reflux overnight, the mixture was concentrated *in vacuo*, diluted with dichloromethane, washed with 1 M hydrochloric acid, then washed with 1 N aqueous sodium hydroxide and dried over anhydrous magnesium sulfate. Filtration and concentration *in vacuo* afforded an oil which was purified by preparative plate chromatography (silica gel) using 2% methanol-dichloromethane and concentrated ammonium hydroxide to provide the title compound (Formula 9.3, (+) -4-(3,10-dibromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-1-[[1-[2,3,4,6-tetra-O-acetyl-1- β -D-glucopyranosyl]-4-piperidinyl]acetyl]piperidine) (0.05 g, 16%).

ASSAYS

FPT IC₅₀ (inhibition of farnesyl protein transferase, *in vitro* enzyme assay) and COS Cell IC₅₀ (Cell-Based Assay) were determined following the assay procedures described in WO 95/10516, published April 20, 1995. GGPT IC₅₀ (inhibition of geranylgeranyl protein transferase, *in vitro* enzyme assay), Cell Mat Assay, and anti-tumor activity (*in vivo* anti-tumor studies) could be determined by the assay procedures described in WO 95/10516. The disclosure of WO 95/10516 is incorporated herein by reference thereto.

Additional assays can be carried out by following essentially the same procedure as described above, but with substitution of alternative indicator tumor cell lines in place of the T24-BAG cells. The assays can be conducted using either DLD-1-BAG human colon carcinoma cells expressing an activated K-ras gene or SW620-BAG human colon carcinoma cells expressing an activated K-ras gene. Using other tumor cell lines known in the art, the activity of the compounds of this invention against other types of cancer cells could be demonstrated.

Soft Agar Assay:

Anchorage-independent growth is a characteristic of tumorigenic cell lines. Human tumor cells are suspended in growth medium containing 0.3% agarose and an indicated concentration of a farnesyl transferase inhibitor. The solution is overlaid onto growth medium solidified with 0.6% agarose

- 68 -

containing the same concentration of farnesyl transferase inhibitor as the top layer. After the top layer is solidified, plates are incubated for 10-16 days at 37°C under 5% CO₂ to allow colony outgrowth. After incubation, the colonies are stained by
5 overlaying the agar with a solution of MTT (3-[4,5-dimethyl-thiazol-2-yl]-2,5-diphenyltetrazolium bromide, Thiazolyl blue) (1 mg/mL in PBS). Colonies can be counted and the IC₅₀'s can be determined.

10 Compounds 2.0, 3.0, 4.0, 5.0, 6.0, and 9.3 had an FPT IC₅₀ (H-ras) within the range of 4.6 to 140nM (nanomolar).

Compounds 4.0, 5.0 and 9.3 had an FPT IC₅₀ (K-ras) within the range of 29 to 91nM.

Compounds 4.0, 5.0, 6.0 and 9.3 had a Cos Cell IC₅₀ within
15 the range of 35 to 120nM.

Compounds 5.0 and 9.3 had a Soft Agar IC₅₀ within the range of 80 to >500nM.

Those skilled in the art will appreciate that when W is a
20 pyranose, pyranoside, furanose or furanoside, acidic conditions (e.g., in the stomach) may result in removal of this W group. Therefore, it would be desirable to protect oral preparations of compounds with these W groups from acidic conditions, e.g., by enteric coating.

25 For preparing pharmaceutical compositions from the compounds described by this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. The powders and tablets
30 may be comprised of from about 5 to about 70 percent active ingredient. Suitable solid carriers are known in the art, e.g. magnesium carbonate, magnesium stearate, talc, sugar, lactose. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration.

35 For preparing suppositories, a low melting wax such as a mixture of fatty acid glycerides or cocoa butter is first melted, and the active ingredient is dispersed homogeneously therein as

by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool and thereby solidify.

Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-
5 propylene glycol solutions for parenteral injection.

Liquid form preparations may also include solutions for intranasal administration.

Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in
10 combination with a pharmaceutically acceptable carrier, such as an inert compressed gas.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such
15 liquid forms include solutions, suspensions and emulsions.

The compounds of the invention may also be deliverable transdermally. The transdermal compositions can take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are
20 conventional in the art for this purpose.

Preferably the compound is administered orally.

Preferably, the pharmaceutical preparation is in unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component, e.g.,
25 an effective amount to achieve the desired purpose.

The quantity of active compound in a unit dose of preparation may be varied or adjusted from about 0.1 mg to 1000 mg, more preferably from about 1 mg. to 300 mg, according to the particular application.

30 The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than
35 the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. For convenience, the total daily

- 70 -

dosage may be divided and administered in portions during the day if desired.

The amount and frequency of administration of the compounds of the invention and the pharmaceutically acceptable salts thereof will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptoms being treated. A typical recommended dosage regimen is oral administration of from 10 mg to 2000 mg/day preferably 10 to 1000 mg/day, in two to four divided doses to block tumor growth. The compounds are non-toxic when administered within this dosage range.

The following are examples of pharmaceutical dosage forms which contain a compound of the invention. The scope of the invention in its pharmaceutical composition aspect is not to be limited by the examples provided.

Pharmaceutical Dosage Form Examples

EXAMPLE A

Tablets

No.	Ingredients	mg/tablet	mg/tablet
1.	Active compound	100	500
2.	Lactose USP	122	113
3.	Corn Starch, Food Grade, as a 10% paste in Purified Water	30	40
4.	Corn Starch, Food Grade	45	40
5.	Magnesium Stearate	3	7
Total		300	700

20 Method of Manufacture

Mix Item Nos. 1 and 2 in a suitable mixer for 10-15 minutes. Granulate the mixture with Item No. 3. Mill the damp granules through a coarse screen (e.g., 1/4", 0.63 cm) if necessary. Dry the damp granules. Screen the dried granules if necessary and mix with Item No. 4 and mix for 10-15 minutes.

- 71 -

Add Item No. 5 and mix for 1-3 minutes. Compress the mixture to appropriate size and weigh on a suitable tablet machine.

EXAMPLE B

5

Capsules

No.	Ingredient	mg/capsule	mg/capsule
1.	Active compound	100	500
2.	Lactose USP	106	123
3.	Corn Starch, Food Grade	40	70
4.	Magnesium Stearate NF	<u>7</u>	<u>7</u>
Total		253	700

Method of Manufacture

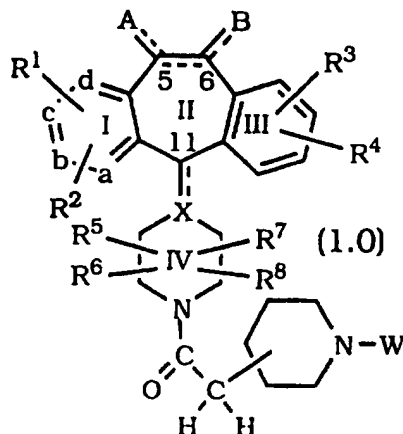
10 Mix Item Nos. 1, 2 and 3 in a suitable blender for 10-15 minutes. Add Item No. 4 and mix for 1-3 minutes. Fill the mixture into suitable two-piece hard gelatin capsules on a suitable encapsulating machine.

15 While the present invention has been described in conjunction with the specific embodiments set forth above, many alternatives, modifications and variations thereof will be apparent to those of ordinary skill in the art. All such alternatives, modifications and variations are intended to fall within the spirit and scope of the present invention.

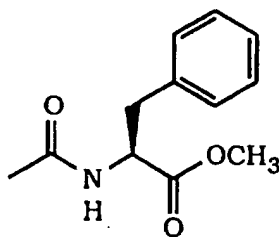
20

WHAT IS CLAIMED IS:

1. A compound of the formula:



- 5 or a pharmaceutically acceptable salt or solvate thereof, wherein:
one of a, b, c and d represents N or NR⁹ wherein R⁹ is O⁻, -CH₃
or -(CH₂)_nCO₂H wherein n is 1 to 3, and the remaining a, b, c
and d groups represent CR¹ or CR²; or
each of a, b, c, and d are independently selected from CR¹
10 or CR²;
each R¹ and each R² is independently selected from H,
halo, -CF₃, -OR¹⁰, -COR¹⁰, -SR¹⁰, -S(O)_tR¹¹ (wherein t is 0, 1 or
2), -SCN, -N(R¹⁰)₂, -NR¹⁰R¹¹, -NO₂, -OC(O)R¹⁰, -CO₂R¹⁰,
-OCO₂R¹¹, -CN, -NHC(O)R¹⁰, -NH₂SO₂R¹⁰, -CONHR¹⁰,
15 -CONHCH₂CH₂OH, -NR¹⁰COOR¹¹.



- SR¹¹C(O)OR¹¹, -SR¹¹N(R⁷⁵)₂ wherein each R⁷⁵ is independently selected from H and -C(O)OR¹¹, benzotriazol-1-yloxy, tetrazol-5-ylthio, or substituted tetrazol-5-ylthio, alkynyl, alkenyl or alkyl, said alkyl or alkenyl group optionally being substituted with halo, -OR¹⁰ or -CO₂R¹⁰;
- R³ and R⁴ are the same or different and each independently represents H, any of the substituents of R¹ and R², or R³ and R⁴ taken together represent a saturated or unsaturated C₅-C₇ fused ring to the benzene ring (Ring III);

- 73 -

R⁵, R⁶, R⁷ and R⁸ each independently represents H, -CF₃, -COR¹⁰, alkyl or aryl, said alkyl or aryl optionally being substituted with -OR¹⁰, -SR¹⁰, -S(O)_tR¹¹, -NR¹⁰COOR¹¹, -N(R¹⁰)₂, -NO₂, -COR¹⁰, -OCOR¹⁰, -OCO₂R¹¹, -CO₂R¹⁰, OPO₃R¹⁰ or R⁵ is combined with R⁶ to represent =O or =S and/or R⁷ is combined with R⁸ to represent =O or =S;

R¹⁰ represents H, alkyl, aryl, or aralkyl;

R¹¹ represents alkyl or aryl;

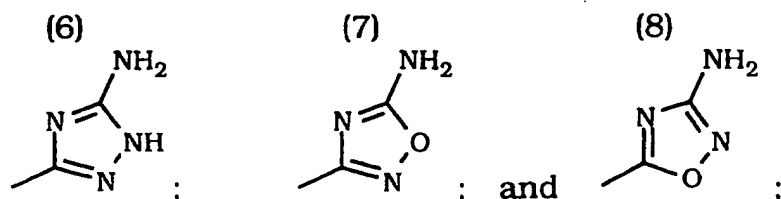
X represents N, CH or C, which C may contain an optional double bond (represented by the dotted line) to carbon atom 11; the dotted line between carbon atoms 5 and 6 represents an optional double bond, such that when a double bond is present, A and B independently represent -R¹⁰, halo, -OR¹¹, -OCO₂R¹¹ or -OC(O)R¹⁰, and when no double bond is present between carbon atoms 5 and 6, A and B each independently represent H₂, -(OR¹¹)₂; H and halo, dihalo, alkyl and H, (alkyl)₂, -H and -OC(O)R¹⁰, H and -OR¹⁰, =O, aryl and H, =NOR¹⁰ or -O-(CH₂)_p-O- wherein p is 2, 3 or 4; and

W represents a heteroaryl, aryl, heterocyloalkyl or cycloalkyl group.

2. The compound of Claim 1 wherein R² is H; R¹ is selected from the group consisting of: Br and Cl; R³ is selected from the group consisting of: Br and Cl; R⁴ is selected from the group consisting of: H, Br and Cl; R⁵, R⁶, R⁷ and R⁸ are H; A and B are each H₂; and the optional bond between C5 and C6 is absent.

3. The compound of Claim 1 or 2 wherein W is selected from the group consisting of:

(A) heteroaryl selected from the group consisting of: (1) 1-phenyl-1H-tetrazol-5-yl; (2) pyridyl; (3) thiazolyl; (4) benzoxazolyl; (5) pyrimidinyl;



- 74 -

(B) heterocycloalkyl selected from the group consisting of: (1) cyclic guanidines; (2) cyclic amidines; (3) five and six membered heterocycloalkyl rings; and (4) pyranosidyl; and

(C) cycloalkyl selected from the group consisting of:
5 cyclopropane, cyclopentane, and cyclohexane.

4. The compound of any of Claims 1-3 wherein R⁴ is H.

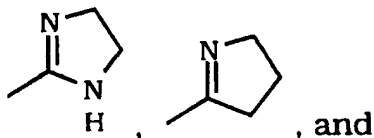
5. The compound of any of Claims 1-3 wherein R⁴ is
10 selected from the group consisting of: Cl or Br.

6. The compound of any of Claims 1-5 wherein X is CH.

7. The compound of any of Claims 1-6 wherein W is
15 selected from the group consisting of:

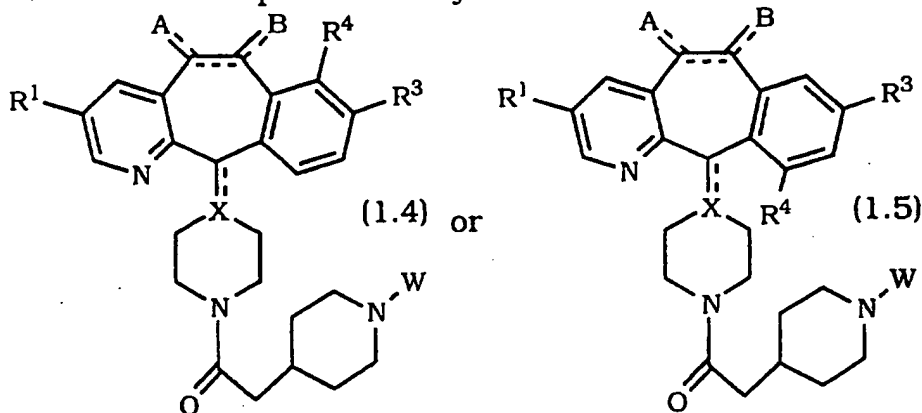
(A) heteroaryl selected from the group consisting of: (1) 1-phenyl-1H-tetrazol-5-yl; (2) pyridyl; (3) thiazolyl; (4) benzoxazolyl; and (5) pyrimidinyl; and

(B) heterocycloalkyl selected from the group consisting
20 of:



2,3,4,6-tetra-O-acetyl-1-beta-D-glucopyranosyl.

8. The compound of any of Claims 1-7 selected from:



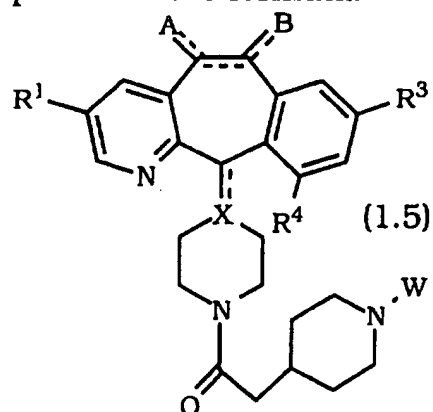
25

wherein R¹, R³ and R⁴ are each independently selected from halo; and A, B, X and W are as defined in Claim 1.

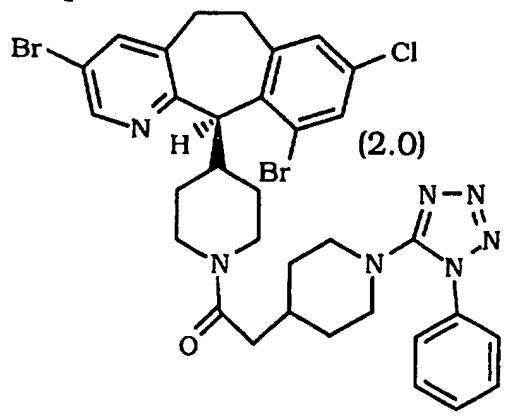
- 75 -

9. The compound of any of Claims 1-8 wherein R^1 is Br; and R^3 is Cl; and R^4 is Br.

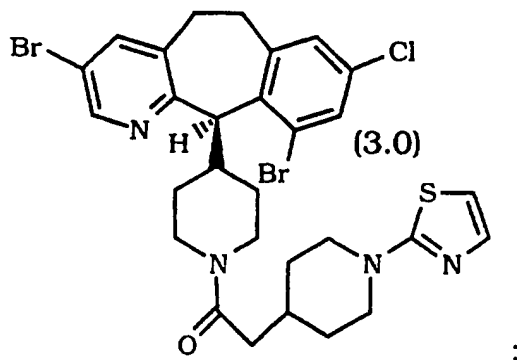
5 10. The compound of any of Claims 1-9 wherein said compound is a compound of the formula:



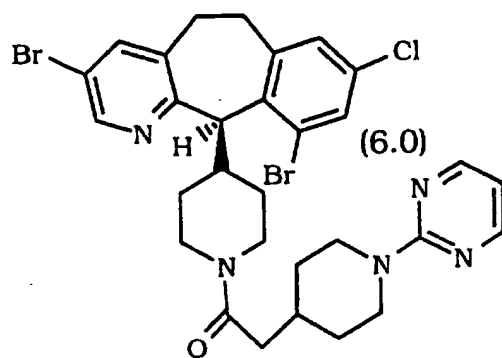
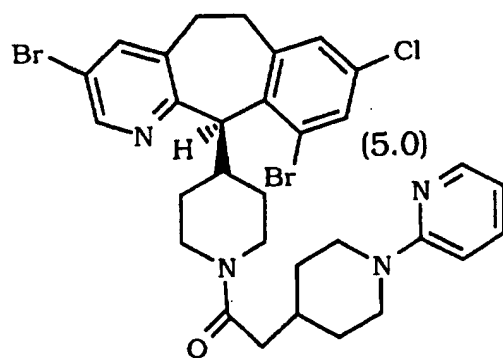
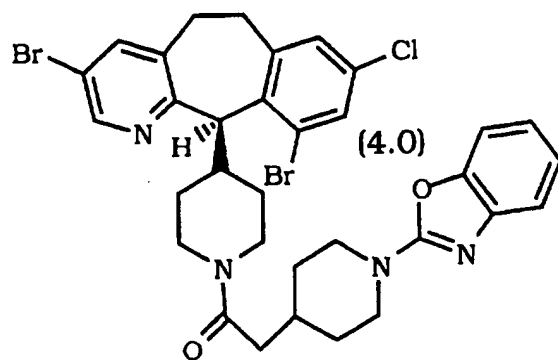
11. The compound of Claim 1 selected from:



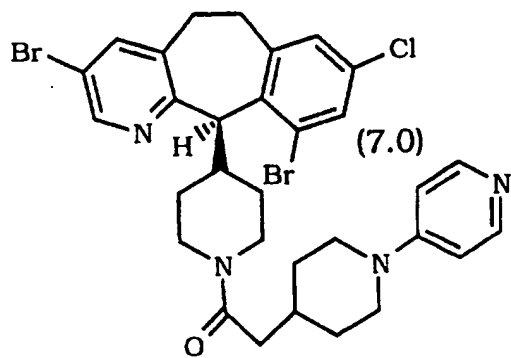
10



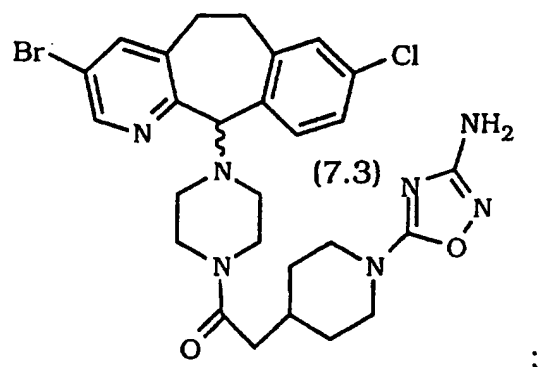
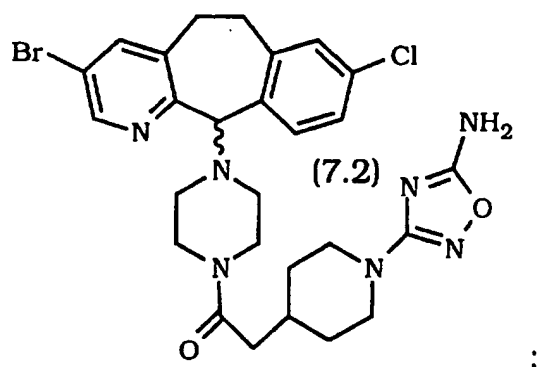
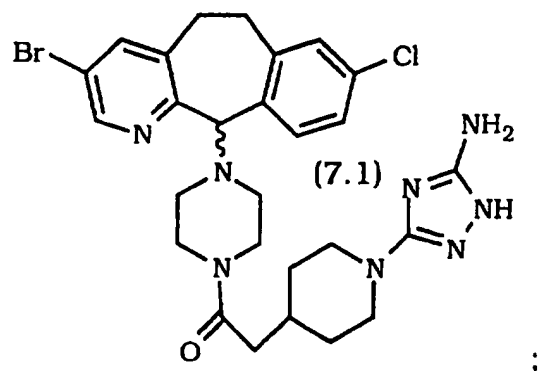
- 76 -



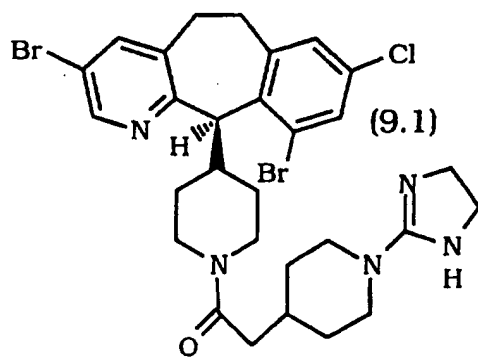
5



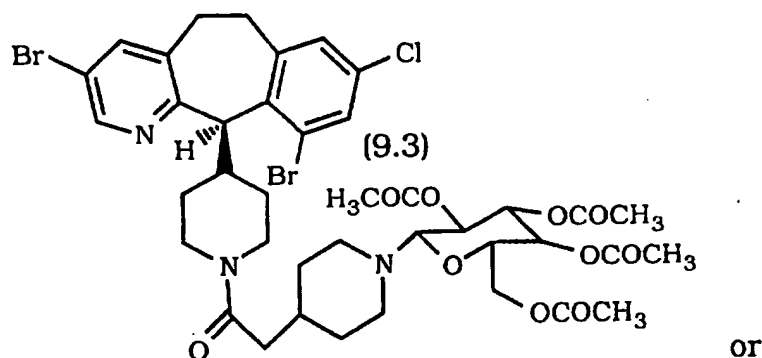
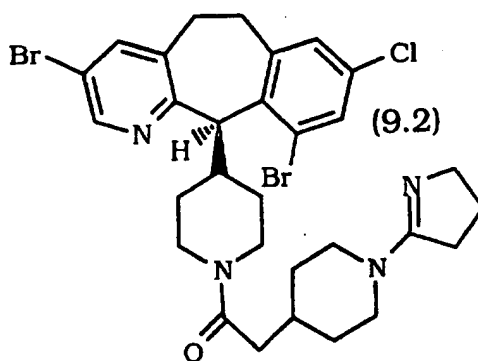
- 77 -



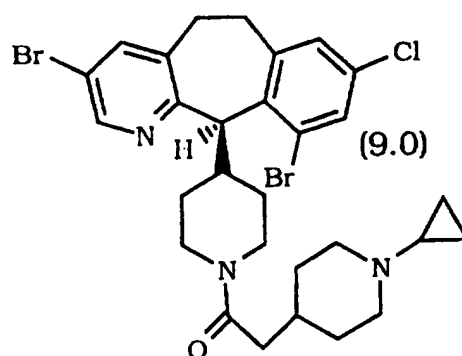
5



- 78 -



or



5

12. A method of treating tumor cells comprising administering an effective amount of a compound of any of Claims 1-11.

10

13. The method of Claim 12 wherein the cells treated are pancreatic tumor cells, lung cancer cells, myeloid leukemia tumor cells, thyroid follicular tumor cells, myelodysplastic tumor cells, epidermal carcinoma tumor cells, bladder carcinoma tumor cells, colon tumors cells, breast tumor cells or prostate tumor cells.

15

- 79 -

14. A method of inhibiting farnesyl protein transferase comprising the administration of an effective amount of the compound of any of Claims 1-11.

5 15. A pharmaceutical composition comprising an effective amount of compound of any of Claims 1-11 in combination with a pharmaceutically acceptable carrier.

10 16. The use of a compound of any of Claims 1-11 for the treatment of tumor cells.

17. The use of a compound of any of Claims 1-11 for the manufacture of a medicament for the treatment of tumor cells.

15 18. The use of a compound of any of Claims 1-11 for the inhibition of farnesyl protein transferase.

20 19. The use of a compound of any of Claims 1-11 for the manufacture of a medicament for the inhibition of farnesyl protein transferase.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 97/15907

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D401/04 A61K31/55

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 95 10516 A (SCHERING CORP) 20 April 1995 cited in the application see the whole document ---	1-11, 15-19
Y	WO 95 10515 A (SCHERING CORP) 20 April 1995 see the whole document ---	1-11, 15-19
Y	WO 95 10514 A (SCHERING CORP) 20 April 1995 see the whole document ---	1-11, 15-19
Y	EP 0 495 484 A (SS PHARMACEUTICAL CO) 22 July 1992 see the whole document ---	1-11, 15-19
-/-		

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

Z document member of the same patent family

Date of the actual completion of the international search

17 December 1997

Date of mailing of the international search report

23.01.98

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl
Fax: (+31-70) 340-3016

Authorized officer

Stellmach, J

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 97/15907

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 396 083 A (SCHERING CORP) 7 November 1990 see the whole document ---	1-11, 15-19
Y	EP 0 270 818 A (SCHERING CORP) 15 June 1988 see the whole document ---	1-11, 15-19
Y	BISHOP, W.R. ET AL.: "Novel Tricyclic Inhibitors of Farnesyl Protein Transferase" J.BIOL.CHEM., vol. 270, no. 51, 22 December 1995, ROCKVILLE PIKE, pages 30611-30618, XP002050604 see the whole document ---	1-11, 15-19
Y,P	WO 96 30363 A (SCHERING CORP) 3 October 1996 see the whole document ---	1-11, 15-19
Y,P	WO 96 30362 A (SCHERING CORP) 3 October 1996 see the whole document ---	1-11, 15-19
Y,P	WO 96 31478 A (SCHERING CORP ; PHARMACOPEDIA INC (US)) 10 October 1996 see the whole document ---	1-11, 15-19
Y,P	WO 97 23478 A (SCHERING CORP) 3 July 1997 cited in the application see the whole document -----	1-11, 15-19

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 97/15907

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9510516 A	20-04-95	AU 7970394 A	04-05-95
		CA 2174104 A	20-04-95
		EP 0723540 A	31-07-96
		HU 76056 A	30-06-97
		JP 8510760 T	12-11-96
		ZA 9407971 A	12-07-96

WO 9510515 A	20-04-95	AU 7930994 A	04-05-95
		CA 2174105 A	20-04-95
		EP 0723538 A	31-07-96
		HU 76066 A	30-06-97
		JP 8510759 T	12-11-96
		ZA 9407970 A	12-07-96

WO 9510514 A	20-04-95	AU 7970294 A	04-05-95
		CA 2173963 A	20-04-95
		EP 0723539 A	31-07-96
		HU 76057 A	30-06-97
		JP 8510445 T	05-11-96
		US 5661152 A	26-08-97
		ZA 9407969 A	12-07-96

EP 0495484 A	22-07-92	CA 2059363 A	19-07-92
		JP 1954463 C	28-07-95
		JP 5059040 A	09-03-93
		JP 6076403 B	28-09-94
		US 5231101 A	27-07-93

EP 0396083 A	07-11-90	US 5089496 A	18-02-92
		AT 114650 T	15-12-94
		AU 643946 B	02-12-93
		AU 5642090 A	29-11-90
		CA 2053903 A	02-11-90
		DE 69014393 D	12-01-95
		DE 69014393 T	01-06-95
		EP 0471750 A	26-02-92
		ES 2064520 T	01-02-95
		IE 66392 B	27-12-95
		IL 94258 A	07-10-94
		JP 4504724 T	20-08-92

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 97/15907

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0396083 A		KR 9509859 B NO 179674 B OA 9521 A WO 9013548 A US 5151423 A US 5438062 A	29-08-95 19-08-96 15-11-92 15-11-90 29-09-92 01-08-95
EP 0270818 A	15-06-88	US 4826853 A AT 116310 T AU 635400 B AU 7285991 A AU 604285 B AU 8336287 A CA 1305147 A CA 1321589 A CS 9104143 A DE 3750929 D DE 3750929 T DK 73193 A DK 354688 A EP 0330673 A EP 0685476 A ES 2068179 T FI 96768 B HK 186396 A IE 65174 B JP 6078316 B JP 2500910 T OA 9546 A PH 26184 A WO 8803138 A US 5089496 A US 5665726 A US 5438062 A ZA 8708128 A	02-05-89 15-01-95 18-03-93 30-05-91 13-12-90 25-05-88 14-07-92 24-08-93 16-09-92 09-02-95 01-06-95 21-06-93 28-06-88 06-09-89 06-12-95 16-04-95 15-05-96 11-10-96 04-10-95 05-10-94 29-03-90 31-01-93 18-03-92 05-05-88 18-02-92 09-09-97 01-08-95 29-04-88
WO 9630363 A	03-10-96	AU 5307796 A	16-10-96
WO 9630362 A	03-10-96	AU 5307696 A	16-10-96

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 97/15907

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9631478 A	10-10-96	AU 5527996 A	23-10-96
WO 9723478 A	03-07-97	AU 1331197 A	17-07-97